Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

JANUARY--1961

Volume 11 - Number 1

101180

THE FACE OF EPILEPSY 1961

Yesterday he handled $268,743.29—some of it may have been yours. The folks at the bank can't say enough about him. Everyone knows it's only a matter of time until he moves up to the Head Teller's window. Only a few short years ago they might have thought twice about hiring him, much less giving him such a responsible position. He is an epileptic. Today he leads a useful, productive life thanks to your increased knowledge and modern pharmaceutical agents. One of our five distinguished anticonvulsants may be just right for your next patient.

PEGANONE® (Ethotoin, Abbott) offers exceptionally low toxicity in the treatment of grand mal and psychomotor seizures.

PHENURONE® (Phenacemide, Abbott) is often effective where other agents fail. Useful in grand mal, petit mal, psychomotor and mixed seizures.

GEMONIL® (Metharbital, Abbott) is relatively non-toxic. For treatment of grand mal, petit mal, myoclonic and mixed seizures symptomatic of brain damage.

TRIDIONE® (Trimethadione, Abbott) and **PARADIONE**® (Paramethadione, Abbott) are homologous agents. They generally afford symptomatic control of petit mal, myoclonic and akinetic seizures.

ABBOTT

Dynamic Myelography

These two radiographs of the same patient demonstrate the bulging of the annulus fibrosus during hyperextension and flexion, respectively, of the vertebral column. 30 cc of ***Pantopaque*** contrast medium was used. Note how this technique permits visualization of the posterior surface of the vertebral canal.

"PANTOPAQUE" *is the registered trademark under which all leading x-ray dealers supply the compound ethyl iodophenylundecylate, which is synthesized by the Research Laboratories of Eastman Kodak Company and prepared as the myelographic contrast medium Iophendylate Injection, U.S.P., by Lafayette Pharmacal Inc. The trademark serves to indicate to the radiologist continuity of experience in the manufacture of this medium.*

DRUG-INDUCED PARKINSONISM IS ON THE RISE,
reflecting the growing use of potent tranquilizers. These extrapyramidal disturbances may be reduced by lowering tranquilizer dosage.

*"It is almost always preferable, however, to merely add oral **AKINETON®**... since this avoids the risk of loss of therapeutic benefit and permits uninterrupted phenothiazine therapy."

AKINETON®

BRAND OF BIPERIDEN

a prompt, specific countermeasure to drug-induced akinesia
motor restlessness · akathisia · torticollis · oculogyric crises · chorea

remarkably safe — "Akineton was not responsible for a single dangerous or toxic effect in the 500 patients treated."*

Dosage: Doses required to achieve the therapeutic goal are variable and individually adjusted. The following are average doses.

Drug-induced extrapyramidal disorders
1 tablet (2 mg.) one to three times daily

Parkinson's disease
1 tablet (2 mg.) three or four times daily

AKINETON hydrochloride tablets—2 mg., bisected, bottles of 100 and 1000.

*Ayd, Frank J., Jr.: Drug-induced Extrapyramidal Reactions: Their Clinical Manifestations and Treatment with Akineton. Psychosomatics 1:143 (May-June) 1960.

KNOLL PHARMACEUTICAL COMPANY, ORANGE, NEW JERSEY

Volume 11 **Neurology** *Number 1*

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

OFFICERS

AUGUSTUS S. ROSE, M.D., *President*
A. L. SAHS, M.D., *President-Elect*
JOSEPH M. FOLEY, M.D., *Vice-President*
ROBERT UTTERBACK, M.D., *Secretary*
CHARLES M. POSER, M.D., *Treasurer*

BOARD OF EDITORS

Editor-in-Chief: RUSSELL N. DEJONG, M.D., *Ann Arbor, Michigan*
Associate Editor: MABEL G. MASTEN, M.D., *Miami, Florida*
Editorial Board: PEARCE BAILEY, M.D., *Washington, D. C.*
ARTHUR L. BENTON, PH.D., *Iowa City, Iowa*
JOE R. BROWN, M.D., *Rochester, Minnesota*
ROLAND P. MACKAY, M.D., *Chicago, Illinois*
H. HOUSTON MERRITT, M.D., *New York, New York*
FRANK MORRELL, M.D., *Minneapolis, Minnesota*
JAMES L. O'LEARY, M.D., *St. Louis, Missouri*
CARL C. PFEIFFER, M.D., *Atlanta, Georgia*
ALFRED POPE, M.D., *Waverly, Massachusetts*
E. P. RICHARDSON, JR., M.D., *Boston, Massachusetts*
RICHARD B. RICHTER, M.D., *Chicago, Illinois*
J. PRESTON ROBB, M.D., *Montreal, Canada*
RAY S. SNIDER, M.D., *Chicago, Illinois*
JAMES E. P. TOMAN, M.D., *Chicago, Illinois*
DONALD B. TOWER, M.D., *Bethesda, Maryland*
ALPHONSE R. VONDERAHE, M.D., *Cincinnati, Ohio*
A. EARL WALKER, M.D., *Baltimore, Maryland*
PAUL I. YAKOVLEV, M.D., *Boston, Massachusetts*

NEUROLOGY is published monthly at 84 So. Tenth St., Minneapolis 3, Minn., by LANCET PUBLICATIONS, INCORPORATED. Subscription rate: $12.00 a year, $1.00 a copy; outside the United States $13.00 a year, $1.10 a copy. Second-class postage paid at Minneapolis, Minn.

in G.I., G.U. and Biliary SPASM

"Murel"-S.A.

Sustained Action Tablets

prompt, continuous and prolonged antispasmodic action for 6 to 9 hours with a single tablet

"MUREL" Advantages[1-4]

- Exceptionally effective clinically because three-way mechanism of action in one molecule (anticholinergic, musculotropic, ganglion-blocking) exerts synergistic spasmolytic effect
- Complementary action permits significantly low dosage and reduces reaction potential of any one mechanism
- Remarkably free from drug-induced complications such as mouth dryness, visual disturbances, urinary retention

Suggested Average Dosage: 40 to 80 mg. daily, depending on condition and severity. The higher range of dosage is usually required in spasm of the genitourinary and biliary tracts. One "Murel"-S.A. Sustained Action Tablet morning and evening. *When anxiety and tension are present,* "Murel" with Phenobarb-S.A. is suggested.

Available as: No. 315—"Murel"-S.A., 40 mg. Valethamate bromide; and No. 319—"Murel" with Phenobarb-S.A., with ½ gr. phenobarbital, present as the sodium salt. Both in bottles of 100 and 1,000.

Also available: "Murel" Tablets No. 314—10 mg. Valethamate bromide; "Murel" with Phenobarbital Tablets No. 318—10 mg. Valethamate bromide and ¼ gr. phenobarbital.

"Murel" Injectable No. 405—10 mg. Valethamate bromide per cc.

Precautions: As with other antispasmodic agents, caution should be exercised in patients with prostatic hypertrophy, glaucoma, and in the presence of cardiac arrhythmias.

References available on request.

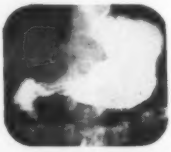
AYERST LABORATORIES
New York 16, N. Y. • Montreal, Canada

for acute, severe episodes
"MUREL" Injectable

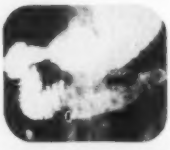
Female patient, age 55, complaining of nausea and epigastric discomfort after meals.

Diagnosis: Hiatus hernia and gastric ulcer.

1 hour after barium administration: Retention of barium due to spasticity of the gastric outlet, and incomplete visualization of the pylorus, duodenum and duodenal sweep. (Some barium has entered the small bowel.)



20 minutes after administration of "Murel" 2 cc. I.V.: Barium entering duodenum and duodenal sweep as spasticity is relieved.



10 minutes later: Good filling of the gastric outlet as well as of the duodenal sweep.

Medical Records of Ayerst Laboratories **6027**

Volume 11 **Neurology** *Number 1*

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

JANUARY 1961 • *Contents*

The Robert Wartenberg Memorial Lecture:
The Volume of the Cerebral Ventricles 1
JAMES W. D. BULL, M.D.

Angiographic Appearances in Acute Intracranial Hypertension 10
H. F. W. PRIBRAM, D.M.R.D.

Oscillometry and Pressure of the Carotid Artery: A Preliminary Report 22
S. DOĞULU, M.D.

Electrolyte Distribution in Mammalian Central Nervous System—
Are Glia High Sodium Cells? 27
ROBERT KATZMAN, M.D.

The Brain ACh-AChE-ChA System in Respiratory Control 37
BERNARD METZ, Ph.D.

Role of the Sympathetic Nervous System in
Urinary Bladder Function in the Cat 46
EVERETT H. INGERSOLL, Ph.D., LOUISE L. JONES, and
ERLING S. HEGRE, Ph.D.

Painful Ophthalmoplegia:
Its Relation to Indolent Inflammation of the Cavernous Sinus 56
WILLIAM E. HUNT, M.D., JOHN N. MEAGHER, M.D.,
HARRY E. LE FEVER, M.D., and WOLFGANG ZEMAN, M.D.

Cerebrovascular Disease:
VI. Relationship to Disease of the Heart and the Aorta 63
A. B. BAKER, M.D., A. IANNONE, M.D., and J. KINNARD, M.D.

(Continued on following page)

NEUROLOGY, copyright 1961 by LANCET PUBLICATIONS, INC. Title registered U. S. Patent Office. Louis M. Cohen, Publisher. Allan Stone, Assistant to the Publisher. Belle Rockwood, Managing Editor. Maurice Wolff, Business Manager, 84 S. 10th St., Minneapolis 3, Minn. ADVERTISING REPRSENTATIVES: *New York 17:* Burt D. Cohen, Lee Klemmer, Bernard A. Smiler, John Winter, 1 E. 42nd St. Telephone: Murray Hill 2-8717. *Chicago 6:* Greg Gelderman, Jay H. Herz, Hugh Gibson, 20 N. Wacker Drive, Suite 1462. Telephone: Central 6-4619. *San Francisco 4:* Duncan A. Scott & Co., 85 Post St., Fifth Floor. Telephone: Garfield 1-7950. *Los Angeles 57:* Duncan A. Scott & Co., 1901 West Eighth St. Telephone: Dunkirk 8-4151.

Contents—*Continued*

Localization of Adenosinetriphosphatase in Capillaries of the Brain as Revealed by Electron Microscopy 71
RICHARD M. TORACK, M.D., MARTIN BESEN, B.S., and NORWIN H. BECKER, M.D.

Selective Head Cooling in the Dog: A Preliminary Report of Technic and Results 77
WILLIAM LEE PRITCHARD, M.D.

Influence of Surgical Procedures on the Course of Multiple Sclerosis 81
ALAN RIDLEY, M.B. (Durh.), M.R.C.P. (Lond.), and KURT SCHAPIRA, M.B., B.S. (Durh.)

Fatal Nucleus Pulposus Embolism of Spinal Cord After Trauma 83
J. LAWRENCE NAIMAN, M.D., WILLIAM L. DONOHUE, M.D., and JOHN STOBO PRICHARD, M.D.

Announcing Chartered Air Transportation for Members of the American Academy of Neurology 88

Book Reviews 90

INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

Manuscripts submitted for publication (other than those read at meetings of the Academy) should be sent to Dr. Russel N. DeJong, University Hospital, Ann Arbor, Michigan. Books for review and business correspondence should be addressed to NEUROLOGY, 84 South Tenth Street, Minneapolis 3, Minnesota. News items related to the American Academy of Neurology or to the field of neurology in general are to be sent to Dr. Pearce Bailey, 4725 Sedgwick, N.W., Washington 16, D. C.

Manuscripts are accepted for publication on condition that they are contributed solely to NEUROLOGY. They must be typewritten, double spaced, and only the original copy should be submitted. Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be unmounted glossy prints. Tables should be typed on separate sheets. The title of the article, name of author, and number of figure should be placed on the back of every illustration, and the top should be designated. Legends for figures should be typed and are not to be attached to the illustrations. If the number of illustrations or tables is excessive, the author will be asked to defray a part of the cost.

References should be designated in the text by superior number, and should be listed at the end of the article in numerical sequence. They should be typed in the following manner:

Journal reference: 1. FRANKLIN, C. R., and BRICKNER, R. M.: Vasospasm associated with multiple sclerosis. Arch. Neurol. & Psychiat. 58:125, 1947.

Textbook reference: 2. WECHSLER, I. S.: A Textbook of Clinical Neurology, ed. 8. Philadelphia, W. B. Saunders Company, 1958, pp. 194-199.

Abbreviations should follow the style of the Quarterly Cumulative Index Medicus.

Galley proofs will be sent to authors for prompt correction. There will be no charge for corrections unless excessive alterations are made. A schedule of charges for reprints will accompany the galley proof.

Because it sustains relief of myasthenia gravis symptoms up to two and one-half times as long as the regular tablet, new MESTINON TIMESPAN often "eliminates the need for sleep interruption to take further medication and leads to better strength in the morning."* For treatment during waking hours, MESTINON TIMESPAN offers greater convenience, prolonged relief on fewer individual doses, and unprecedented freedom from muscarinic side effects.

DOSAGE: Timespan tablets – ½ to 3 tablets once or twice daily.

HOW SUPPLIED: Tablets, 180 mg each – bottle of 100.

*K. R. Magee and M. R. Westerberg, **Neurology**, 9:348, 1959.

p-r-o-l-o-n-g-e-d relief in myasthenia gravis

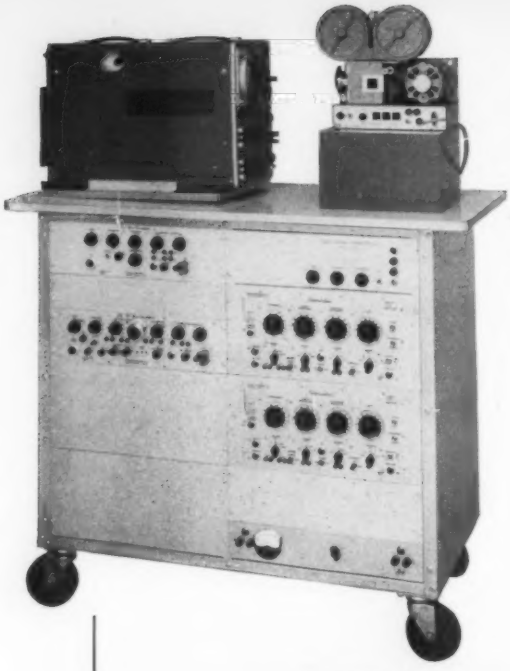
Schematic drawing of nerve endings in striated muscle tissue. By inhibiting destruction of acetylcholine at this junction, Mestinon acts specifically to reestablish neuromuscular control and relieve symptoms of myasthenia gravis.

MESTINON® BROMIDE
—brand of pyridostigmin bromide
(3-hydroxy-1-methylpyridinium bromide)
TIMESPAN®

MESTINON TIMESPAN

in sustained release tablets — requires fewer individual doses

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey



SPECIFY

GRASS
INSTRUMENTS
FOR
PHYSIOLOGICAL
RESEARCH
AND
CLINICAL
APPLICATION

SHOWN ABOVE

- IT 1 RACKMOUNT INSTRUMENT TABLE
- C 4 KYMOGRAPH CAMERA
- S 4 STIMULATOR, RESEARCH MODEL
- P 5 A.C. PRE-AMPLIFIER
- P 6 D.C. PRE-AMPLIFIER WITH HIGH IMPEDANCE INPUT
- AM 3 AUDIO MONITOR
- BC 3 BATTERY CHARGER

OTHER INSTRUMENTS

- S 5, SD 5 AND S 6 STIMULATORS, SIMPLIFIED FOR STUDENT USE
- SIU 4 STIMULUS ISOLATION UNIT
- BPS 1 BRIEF PULSE STIMULATOR
- PS 2 PHOTOSTIMULATOR WITH DELAYED FLASH
- PS 3 CLINICAL PHOTOSTIMULATOR
- LM 1 RF LESION MAKER
- P 8 AND P 9 MINIATURIZED PREAMPLIFIERS
- FT.03 AND FT10 FORCE TRANSDUCERS
- PT 5 AND CP 1 VOLUMETRIC TRANSDUCERS
- TM 1 TRANSDUCER MIXER
- CONTROL CIRCUIT FOR OXIMETER EARPIECE AND CUVETTE
- MODEL 5 POLYGRAPH
- MODELS III, IV AND 6 ELECTROENCEPHALOGRAPHS
- REGULATED POWER SUPPLIES FOR ELECTROENCEPHALOGRAPHS AND PREAMPLIFIERS

GRASS INSTRUMENT COMPANY

101 OLD COLONY AVENUE - QUINCY, MASS.

INSTRUMENT MAKERS TO THE MEDICAL PROFESSION SINCE 1935

D001Q2

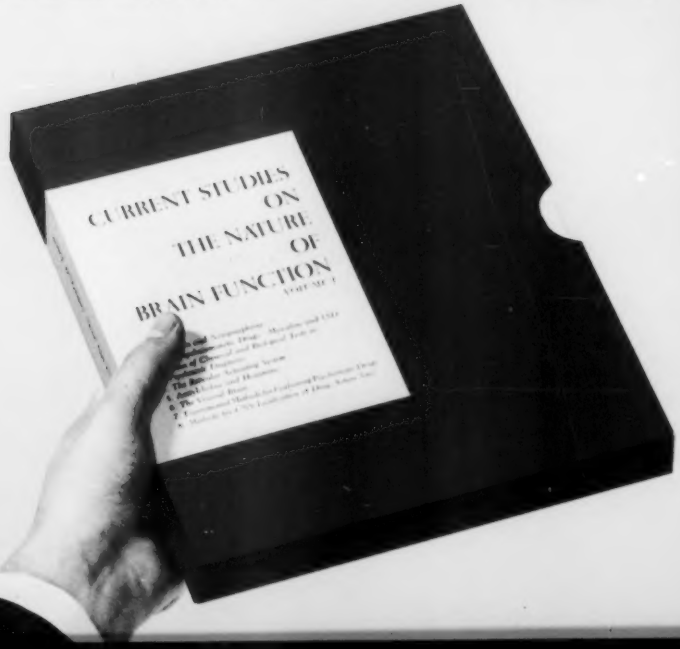
Schering

to fill many gratifying requests
and for your more
convenient reference
—a new printing
in a convenient carrier
—of Studies 1 through 8
in the Brain Function Series

CURRENT STUDIES ON
THE NATURE OF
BRAIN FUNCTION

1. *Serotonin and Norepinephrine*
2. *The Psychotomimetic Drugs — Mescaline and LSD*
3. *Status of Chemical and Biological Tests in Psychiatric Diagnosis*
4. *The Reticular Activating System*
5. *Acetylcholine and Histamine*
6. *The Visceral Brain*
7. *Experimental Methods for Evaluating Psychotropic Drugs*
8. *Methods for CNS Localization of Drug-Action Sites*

—available through your Schering representative or write Schering



Schering

a more effective
phenothiazine

Trilafon®

perphenazine

easily adaptable
to a wide range
of psychotic symptomatology

"Perphenazine is effective in the treatment and management of acute schizophrenia and acute schizoaffective disorders, and for controlling excitement, anxiety, agitation, belligerence, and aggressive behaviour in chronic schizophrenia and other forms of chronic psychosis. The drug helps to relieve anxiety, tension, and depression in psychosomatic disorders and physical illnesses or disabilities."*

Available for psychiatric use as Tablets, Injection, Liquid Concentrate. Consult Schering literature for indications, dosage and administration, precautions and contraindications.

*Rees, L.: Brit. M. J. 2:522, 1960.

If you do not receive this new compilation of the collected "Current Studies on the Nature of Brain Function" within a few weeks, please write "Current Studies" on your stationery and send to Schering Corporation, Bloomfield, N. J. Your copy will be forwarded immediately.

8-723

"the most effective drug against tremor..."[1]

IN PARKINSONISM Parsidol exceeds all other drugs for reducing tremor,[1] a major impairment in this disease. Parsidol also lessens rigidity, brightens the patient's mood and contributes to restoration of self-confidence. Especially well tolerated by older patients,[1,2,3] Parsidol is effective alone, and most patients respond well to a maintenance dosage of 50 mg. q.i.d. Parsidol is compatible with other antiparkinsonian drugs and can be given in combination if so desired.

PARSIDOL®

brand of ethopropazine hydrochloride

PARKINSONISM

WARNER CHILCOTT
MORRIS PLAINS, N.J.

1. Schwab, R. S. and England, A. C.: *J. Chron. Dis. 8*:488 (Oct.) 1958.
2. Schwab, R. S.: *Geriatrics 14*:545 (Sept.) 1959.
3. Doshay, L. J. *et al.*: *J.A.M.A. 160*:348 (Feb. 4) 1956.

PAR-GP04

IN THE SAME PATIENT...

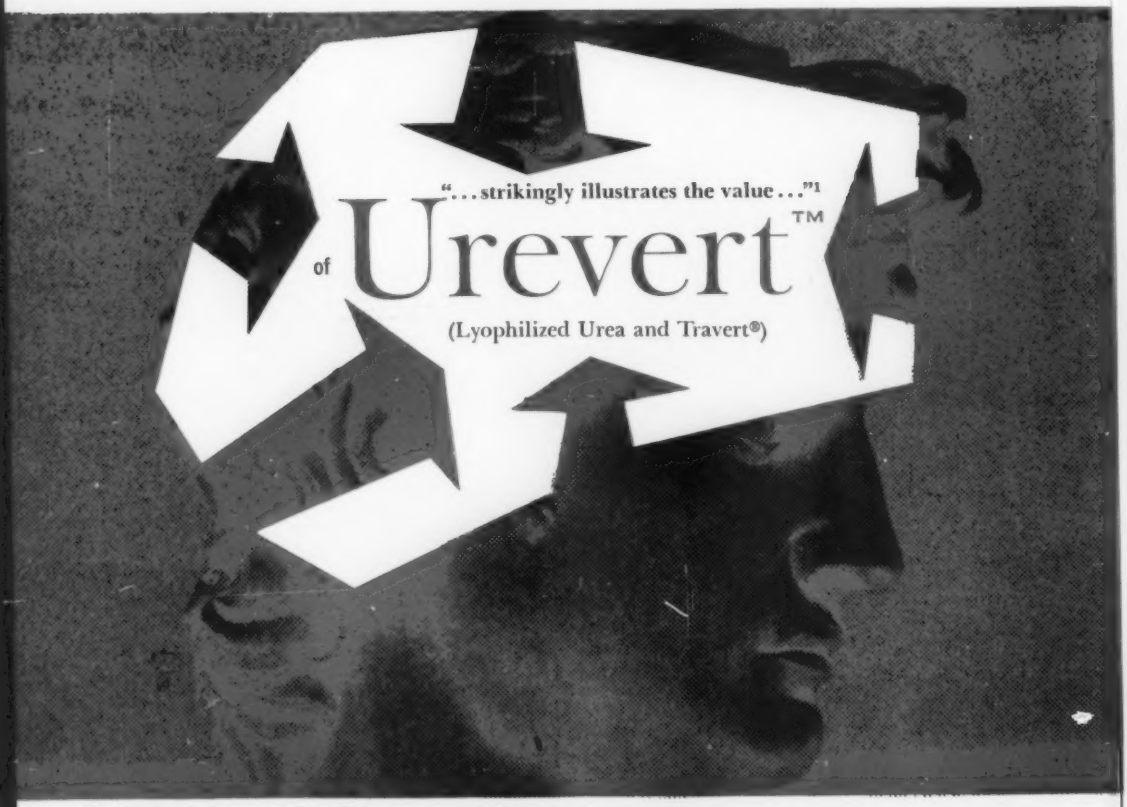
WITHOUT UREVERT

"Prior to the use of urea for intracranial decompression . . . the patient was admitted for cranioplasty because of a left cranial defect. During the operation the brain began to expand . . . it was necessary to reduce . . . pressure by lumbar puncture. The total operating time was two hours and twenty minutes."[1]

WITH UREVERT

"Recently this patient was readmitted for cranioplasty of the right side. In this operation urea [Urevert] was used.... Cranioplasty was easily accomplished. No lumbar puncture was necessary. The operating time was fifty minutes."[1]

CRANIOPLASTY OPERATION TIME WAS REDUCED BY 1-1/2 HOURS!



The New, Superior[1,2] Intracranial Decompressant

"The use of urea [Urevert] for brain decompression often simplifies and extends the limits of neurosurgical procedures and, in some patients, proves to be life-saving."

New Sound-Color Film—The new approach to the reduction of intracranial pressure with Urea-Invert sugar (Urevert) is herein described and illustrated. Conditions so treated include glioblastoma multiforme, optic nerve glioma, frontotemporal meningioma, cerebellar astrocytoma and retrogasserian rhizotomy. Film showings may be arranged by writing to Medical Film Library, Travenol Laboratories, Inc., Morton Grove, Illinois.

1. Taheri, Z. E.: Urevert in Cranial Trauma and Brain Surgery, J. Internatl. College of Surgeons 32:389 (Oct.) 1959.
2. Javid, M.: Urea—New Use of an Old Agent, Reduction of Intracranial and Intraocular Pressure, The Surgical Clinics of North America, Philadelphia, W. B. Saunders Company, Aug. 1958, p. 907.

TRAVENOL LABORATORIES, INC.

Pharmaceutical Products Division of
BAXTER LABORATORIES, INC.
Morton Grove, Illinois

"R Day"

for the neuritis patient can be tomorrow

"R Day"—*when pain is relieved*—can come early for patients with inflammatory (non-traumatic) neuritis if treatment with Protamide is started promptly after onset.

Protamide is the therapy of choice for either early or delayed treatment, but early use assures greatest efficacy.

For example, in a 4-year study[1] and a 26-month study[2] a combined total of 374 neuritis patients treated with Protamide during the first week of symptoms responded as follows:

60% required only 1 or 2 daily injections for complete relief

96% experienced excellent or good results with 5 or less injections

Thus, the neuritis patient's first visit—especially an early one—affords the opportunity to speed his personal "R Day."

Protamide is available at pharmacies and supply houses in boxes of ten 1.3 cc. ampuls. Intramuscularly only, one ampul daily.

PROTAMIDE®

REFER TO PDR

PAGE 813

Sherman Laboratories

Detroit 11, Michigan

1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.

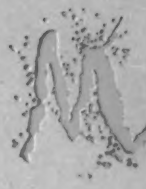
2. Smith, Richard T.: New York Med. 8:16, 1952.

how does* Mellaril *differ from other potent tranquilizers?

Mellaril®

THIORIDAZINE HCl

specific, effective tranquilizer



provides highly effective tranquilization,
relieves anxiety, tension, nervousness,
but is virtually free of such toxic effects as

jaundice
Parkinsonism
blood dyscrasia
dermatitis

greater specificity of tranquilizing action results in fewer side effects

Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action—divorced from such "diffuse" effects as anti-emetic action.

"The most striking aspect of thioridazine [MELLARIL] therapy is the poverty of side-effects."

"In conclusion it may be said that thioridazine is at least as effective in relieving psychiatric illness as other drugs of its class. On a milligram for milligram basis it has the same order of potency as chlorpromazine. In its low incidence of side-effects and toxicity, it is superior to all other tranquilizing drugs tested. For this reason it is well tolerated by patients, particularly those who are not hospitalized and who frequently discontinue their medication with other drugs because of dizziness, sleepiness, increased tension, or Parkinsonism."*

Supply: MELLARIL Tablets, 10 mg., 25 mg., 100 mg.

SANDOZ

*Kinross-Wright, J.: Newer phenothiazine drugs in treatment of nervous disorders. J.A.M.A. 170:1983, July 11, 1959.

when
"Parkinson"
reactions
threaten
in
ataractic
therapy...

add...

ARTANE®

Trihexyphenidyl HCl Lederle

ARTANE is repeatedly cited[1-4] as an effective adjunct to counter parkinsonoid side effects of phenothiazine therapy . . . to forestall withdrawal and secure the benefits of undiminished, uninterrupted, high-dosage therapy.

In Parkinson's disease, ARTANE remains a drug of choice in the experience of many practitioners. Unexcelled for sustained, continuing control of rigidity and tremors, suppression of other symptoms with low risk of untoward effects.

Elixir, 2 mg./5 cc. tsp.

Dosage: 1 mg. first day, gradually increased according to response, to 6-10 mg. daily in 3 divided doses at mealtimes.

1. Critchley, M.: **British, M. J.**, 2:1214 (Nov. 15) 1958.
2. England, A. C., and Schwab, R. S.: **A.M.A. Arch. Int. Med.** 104:439 (Sept.) 1959.
3. Judah, L.: Murphree, O., and Seager, L.: **Am. J. Psychiat.** 115:118 (June) 1959.
4. Pennington, V. M.: **M. Times** 87:1432 (Nov.) 1959.

LEDERLE LABORATORIES,
Pearl River, New York
A Division of AMERICAN CYANAMID COMPANY

Neurology Volume 11 • Number 1

The Robert Wartenberg Memorial Lecture
The volume of the cerebral ventricles

James W. D. Bull, M.D., F.R.C.P., F.F.R.

IT IS A SINGULAR HONOR for a radiologist to be invited to give the Robert Wartenberg Memorial Lecture. I never had the good fortune to meet Dr. Wartenberg, but recently I have tried to form a picture of the man and his work. There cannot have been many personalities in medicine—or for that matter in any other field—who in their fiftieth year moved to another country, or rather subcontinent, with a different native tongue, and rose to the top of the tree. But this was the story of Robert Wartenberg. One has only to glance at the *Festschrift*[1] dedicated to him on the occasion of his sixty-fifth birthday in 1952 to understand with what great respect and affection he was held in this country. Neurologists from all over the world contributed to that special number, which also included a bibliography of the 134 papers which up to that time had come from his pen; the latter two-thirds were written in English after he had moved to this country.

In choosing a subject for this lecture, I was anxious that it should be related in some way to his interests. Wartenberg was one of the first in Europe to make use of pneumoencephalography, and between the years 1923 and 1931 he published 9 papers on the subject. In 1918, when Dandy introduced pneumography, Wartenberg had not yet qualified in medicine and for the next few years that part of Europe from which he came was in havoc. In spite of these difficulties, within five years of Dandy's discovery he had already published a paper on the technic of lumbar encephalography.

The cerebral ventricles have interested, and indeed fascinated, physicians since the beginning of the written history of medicine. At the time of Hippocrates, they were said to be the seat of the human spirit—pneuma animalis. As Bruijn[2] stated: "The ancients could not suspect that some millennia after their glorious era, the human cerebral ventricles would indeed be filled with pneuma, i.e. air, in many cases, be this in an artificial and not in a natural way."

For over forty years now, air has been introduced into the cerebral ventricles as a diag-

From the Department of Radiology, The National Hospital, Queen Square, London.

Read at the twelfth annual meeting of the American Academy of Neurology, Miami Beach, April 30, 1960.

nostic procedure. Nevertheless, we are still unable to measure the volume accurately during life and loose conclusions continue to be made from insufficient radiologic data, seldom backed up by firmly based histologic evidence which can be satisfactorily correlated with clinical findings.

It was Leonardo da Vinci who first studied the anatomy of the cerebral ventricles, but we have no record that he attempted to measure their volume. Some four hundred years later, Welcker[3] made a moderately accurate cast from beeswax, but there was no indication in his paper that he measured the volume. Nor yet did Retzius[4] record the volume of his famous cast made in Wood's metal.

The anatomist Harvey[5] of the University of California appears to have been the first to make volumetric measurements. He took 10 fixed brains, cut each into 4 sections, made casts from individual sections, and then synthesized each ventricular system. The volume varied from 8.9 cc. to 70.7 cc. He stated that no data of age or cause of death were available, but the presumptive age varied from 40 to 70 years. Brück[6] of Germany made 21 ventricular casts; some of the brains were thought to be normal, and others were definitely pathologic, but he gave no figures. He concluded that the normal volume of the ventricular system was 17.8 cc. and that it was moderately constant. Morel and Montmollin[7] of Geneva measured the volumes of 121 brains at post mortem. Their method consisted in first fixing the brains in formalin, then amputating the brain stem at the level of the corpora quadrigemina and making a sagittal section between the hemispheres through the septum lucidum. Each lateral ventricle, having been drained of fluid, was filled with water from a graduated syringe and thus the volume was measured. The combined capacity of the two lateral ventricles varied from 5.5 to 81 cc. The great bulk of the material was pathologic, the patients having suffered from the following diseases: general paralysis of the insane, presenile dementia, chronic hallucinatory psychoses, cerebral atherosclerosis, Alzheimer's disease, and Pick's disease. No correlation was found between the volume of the ventricular system and the weight of the hemispheres. As a general rule, the volume of the ventricles increased with age, but some patients over the age of 80 years had small ventricles.

Quite the most accurate and classic work was carried out by Last and Tompsett.[8] Their superb ventricular casts (from 24 adult and 5 fetal brains) may be seen in the Museum of the Royal College of Surgeons in London. Last and Tompsett took great care to eliminate the factor of shrinkage after fixing their brains, finding that the average amounted to less than 2%. It is very unlikely that any of their predecessors had paid as much care and attention to this important factor. The casts were made from Marco resin 26 C. All the adult brains were assumed to be normal on the evidence that [1] the material was obtained at random from autopsies in which the pathologist had no wish to examine the brain, a fact which emphasized the presumptive normality of the intracranial content, and [2] no unusual features were found in any of the specimens during the careful removal of the brain substance from around the casts. There were 14 male and 10 female adult brains; the ages varied between 29 and 73 years, the average being 51 years. The volume of the smallest cast was 7.4 cc. and that of the largest 56.6 cc., the average being 22.4 cc. Like Morel and Montmollin, they found no relationship betwen the volume of the casts and that of the brain.

More recently, Knudsen[9] of Denmark measured the ventricular volume of 183 brains, all of which were regarded as being grossly normal. He had previously excluded any brain showing severe atherosclerosis in the basal vessels or pronounced gyrus atrophy; in addition, the clinical records were perused and brains from patients with a history of cerebral lesions and clinically marked cerebral arterial sclerosis were also excluded. The ages of the patients varied from 20 to 90 years; 85 brains were from males and 98 from females. In the majority of cases, only the volume of the lateral ventricles was measured, but he found that the average volume of the third ventricle was 0.65 cc. and that of the fourth ventricle 0.85 cc. The volume of the aqueduct of Sylvius was not mentioned but can be assumed to be negligible. He determined the volume by

measuring the amount of air that the ventricles could hold. The brains were cut coronally into blocks, and each block was placed in an apparatus consisting of 2 plates made of transparent plastic and provided with holes which could be plugged. The brain block, which was held between the plates by light pressure applied by wing nuts at each corner, was immersed in water. The plugs were then removed, and the air escaping through the holes was collected in a measuring device consisting of a funnel connected to a graduated tube filled with water. The accuracy of this method was controlled in a number of cases by a subsequent determination of the volume by making an agar cast and the volume of a few of the third and fourth ventricles was determined by the agar method only. Knudsen found that the average volume of a lateral ventricle was 7 cc., but the variation was considerable; the smallest was less than 2 cc. and the largest 39 cc. The volumes were clearly tabulated on a graph (Fig. 1). There was some increase in size of the lateral ventricles with advancing age, but this finding was by no means consistent and Knudsen made the statement: "The opinion that the volume of the lateral ventricle increases with advancing age is, therefore, correct only with qualifications." He further found that the difference in size between the right and left lateral ventricles was negligible in 37% of brains; in 48%, the left lateral ventricle was larger than the right, and, in 15%, the right was larger than the left. He also confirmed that there was no correlation between the weight of the hemispheres and the volume of the lateral ventricles or between any linear dimensions and volume. He thought that measurements of the body of the ventricles at the level of the foramen of Monro and at the posterior border of the splenium of the corpus callosum gave the most satisfactory correlation with the volume.

DISCUSSION ON ANATOMIC FINDINGS

Apparently, there are only 2 large anatomic series in the literature in which the ventricular volumes from normal brains have been measured. Of the 2, Knudsen's is by far the larger, but his methods would seem to be considerably less accurate than those of Last and Tompsett. Nevertheless, the volumetric findings in the 2 series are very comparable. Thus, Knudsen stated that the average volume of a lateral ventricle was 7 cc. Assuming that the volume of the 2 ventricles is about equal (and

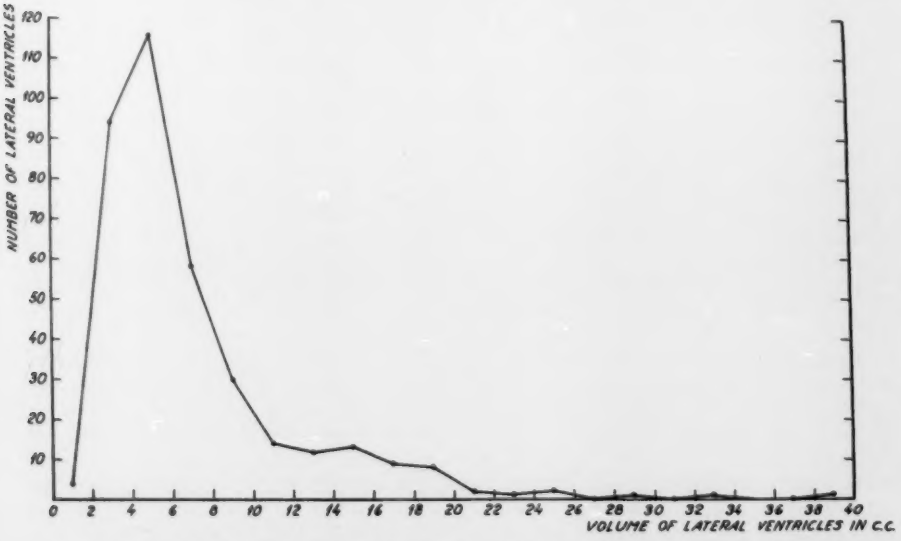


Fig. 1. Graph to show volumes of 366 lateral ventricles (183 brains). From Knudsen[9]

Knudsen positively stated that they were precisely so in 37% of cases), we have an average volume for the 2 lateral ventricles of 14 cc. Examination of Last and Tompsett's casts shows that the 2 lateral ventricles were strikingly symmetric, apart from the posterior horns. Knudsen found that the average volume of the third and fourth ventricles combined was 1.5 cc. This would give a total volume of 15.5 cc. for the ventricular system, and it is clear from his graph that only in very few cases did the combined volume of the 2 lateral ventricles exceed 30 cc.

In any branch of medicine, it is very dangerous to be dogmatic regarding "normal" values, and, if we now turn to Last and Tompsett's figures, with 30 cc. in mind as the upper limit of normal, we find only 4 out of 24 of their casts exceeding this value, (Cast 2, 55.3 cc.; Cast 4, 56.4 cc.; Cast 10, 33 cc.; Cast 12, 56.6 cc.). They found an average value of 22.4 cc., but, if we exclude the above 4 cases, we arrive at an average of 16.8 cc., a figure almost identical to Knudsen's 15.5 cc. Allowing for the fact that Last and Tompsett's method is considerably more accurate, the higher figure is more acceptable. On the other hand, Knudsen's series was very much larger.

In spite of giving very detailed linear and volumetric measurements in their paper, Last and Tompsett did not mention the volume of the third ventricle, aqueduct, or fourth ventricle. Recently, Dr. Tompsett[10] kindly measured the volume of the third ventricle–aqueduct–fourth ventricle complex of his 24 casts. He wrote to me as follows: "I used the method of weighing each cast in air, and then with the third and fourth ventricles immersed in water. The difference in weight of the ventricles under these conditions gives their volume. Owing to the difficulty of immersing the whole of the third and fourth ventricles in water a certain amount of common sense estimation was used to get the figures. For example, when it was possible to immerse four-fifths of the ventricles, an allowance of one-fifth was added to the volume. I think the figures are reasonably accurate. A rough check could be made by comparing similar third and fourth ventricles in cases where in one system the whole could be immersed and in the other only partial immersion was possible. I note that from comparison with the figures we previously published (1953) of the volume of the whole ventricular system, it does not invariably follow that where the total volume of all the ventricles is large, the volume of the third and fourth ventricles is correspondingly great."

The table, compiled from Last and Tompsett's figures, shows [1] the volumes of the third ventricle–aqueduct–fourth ventricle complex in the 24 cases, [2] the total capacity of the ventricular system in each case, and [3] the percentage of the volume occupied by the third ventricle–aqueduct–fourth ventricle complex.

MEASUREMENTS IN LIFE

Indirect methods of measurement of volume have also been attempted. At ventriculography, the amount of cerebrospinal fluid withdrawn and the amount of air introduced can theoretically be measured. In practice, this is extremely difficult because some of the fluid tends to be lost and often a mixture of air and fluid bubbles back after the air has been introduced. Various difficulties are also encountered at air encephalography. Here, it is easy to measure the amount of cerebrospinal fluid withdrawn and also easy to measure the amount of air introduced, but one can never be absolutely certain how much air enters the ventricualr system and how much goes into the subarachnoid space.

Now that anatomists have established that the great majority—perhaps about 90%—of normal ventricular systems have a capacity of not more than about 30 cc. and sometimes as little as 7 cc., it is appropriate to consider how ventricular volumes can be assessed in life.

Radiologic methods of measurement. As far as I am aware, no radiologic method of determining volume has yet been devised. This is hardly surprising when one considers the bizarre shape of the ventricular system. However, criteria have been laid down for the "normal" size, and we must consider their validity.

In 1942, Evans[11] described an encephalographic ratio for estimating ventricular size. He measured the transverse diameter of the anterior horns of the lateral ventricles and

CASTS OF CEREBRAL VENTRICLES
(From Last and Tompsett[9])

Cast number	1	2	3	4	5	6	7	8	9	10	11	12
Volume (cc.) of third ventricle–aqueduct–fourth ventricle	1.0	1.5	1.1	3.1	1.2	0.6	1.1	0.7	1.6	1.0	0.6	0.9
Total volume (cc.) of ventricles	16.3	55.3	19.1	56.4	27.5	8.2	25.5	11.1	26.6	33.0	7.4	56.6
Per cent volume occupied by third ventricle–aqueduct–fourth ventricle	6.1	2.7	5.8	5.5	4.4	7.3	4.3	6.3	6.2	3.0	8.1	1.6

Cast number	13	14	15	16	17	18	19	20	21	22	23	24
Volume (cc.) of third ventricle–aqueduct–fourth ventricle	1.2	0.8	1.2	1.4	1.7	1.2	1.3	1.4	1.5	0.7	1.0	0.8
Total volume (cc.) of ventricles	10.9	18.4	19.4	18.4	20.4	11.2	13.3	14.2	20.3	28.7	7.6	12.5
Per cent volume occupied by third ventricle–aqueduct–fourth ventricle	11.0	4.3	6.2	7.6	8.3	10.7	9.7	9.7	7.4	2.5	13	6.4

related this to the width of the skull (measuring from the inner table), thus obtaining a ratio. The normal range, he said, lay between 0.16 and 0.29, the average being 0.23. The shortcomings of this encephalographic ratio are seen in Last and Tompsett's casts. Their smallest cast (No. 11), with a volume of 7.4 cc., had a maximum spread of the anterior horns of 4.3 cm. In the third largest cast (No. 2), where the ventricular volume was 55.3 cc., the maximum spread of the anterior horns was 4.4 cm. or only 1 mm. greater than the smallest cast. Nevertheless, the volume difference was more than sevenfold. On examination of these 2 casts (Fig. 2), it is obvious that the main bulk of the volume resides in the bodies of the lateral ventricles. Yet other linear measurements, such as the spread of the temporal horns or the anteroposterior length of the lateral ventricles are quite unrelated to the volume.

In more recent years, several writers have drawn attention to the fact that the size of the body of the lateral ventricle is most closely related to its volume. Various measurements of the bodies have been taken in the coronal plane, but they have not been related to any particular volume measurement. In my opinion, the minimum thickness of the body of the ventricle (one of the many measurements listed by Last and Tompsett) is the most important measurement. In practice, this thickness is represented by the width of the floor of the body of the ventricle. I took the mean value of the minimum thickness of the body of each pair of ventricles in Last and Tompsett's series (none of which differed by more than 2 mm.) and plotted it against the volume of the ventricles. The resulting graph (Fig. 3) shows that there is some relationship between the linear and volumetric measurements and allows one to predict the volume of any given ventricular system to within not unreasonable limits. Furthermore, extrapolation gives one some estimate of the volume of enlarged ventricles as recorded on pneumograms. Needless to say, a small correction is necessary in obtaining the true width of the body of the lateral ventricle when taking measurements from a radiograph. The factor depends mainly on the focal-film distance. I was unable to find any other linear measurement which related to the volume as satisfactorily as the minimum thickness of the body.

Having obtained a rough measurement of the volume by this means, one can make a further check by comparing any given antero-

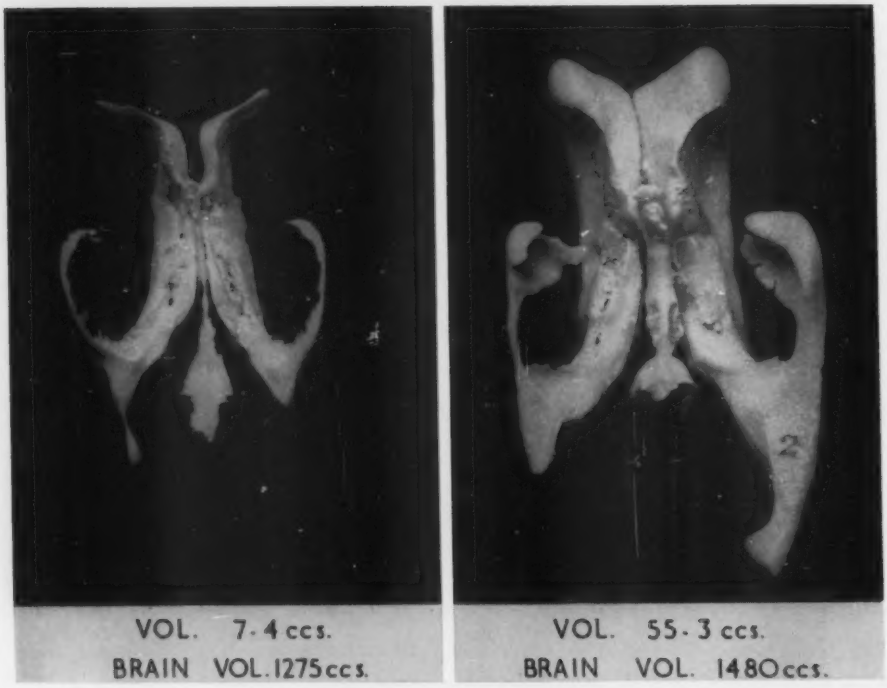


Fig. 2. Photographs of 2 of Last and Tompsett's[8] casts. Note that the spread of the anterior horns is almost identical (see text) but that the spread of the ventricular bodies is quite different.

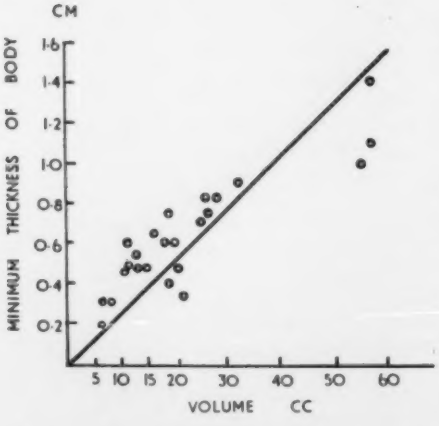


Fig. 3. Graph prepared from Last and Tompsett's[8] measurements. (See text)

posterior pneumograph from life with anteroposterior radiographs of Last and Tompsett's 24 casts. Marco resin provides a quite satisfactory shadow on radiography, and I have taken anteroposterior radiographs of all their casts. It is a fairly simple task to match a cast of known volume against the unknown. Here, no correction for the focus-film distance is necessary as the radiograph of the casts were taken under geometric conditions identical to those in life (Fig. 4).

Radiologic applications. With the normal volume range in mind, it becomes immediately obvious that only relatively small amounts of air are required for lumbar encephalography in most cases. The blind introduction of 100 cc. or more with equivalent drainage of cerebrospinal fluid becomes quite inadmissable. The average normal ventricular system has a capacity of less than 20 cc., and, in practice,

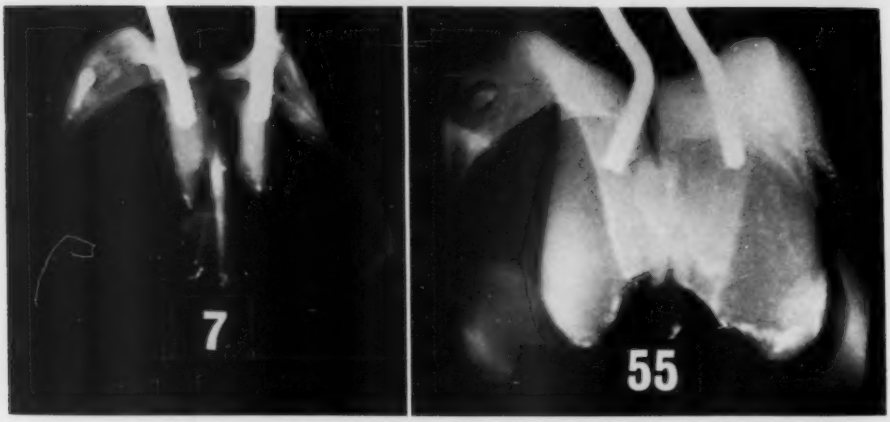


Fig. 4. Radiographs of Last and Tompsett's[8] casts shown in Figure 2. [Left] 7.4 cc. and [Right] 55.3 cc. Note that the main difference lies in the size of the bodies of the lateral ventricles. The anterior horns in illustration at left were so slender that the shadow cast was negligible and cannot, in fact, be seen at all in the reproduction. The two metal rods in each ventricular system are necessary for mounting the casts.

it is very difficult to fill much more than half of the system with air even if one introduces as much as 200 cc. Our method, following that of Robertson,[12] is to introduce about 7 to 10 cc. in the first instance and always under radiographic control, so-called controlled fractional air encephalography (Fig. 5). The initial radiograph often gives one a very good impression of the size of the ventricles, and, in most cases, it is unnecessary and indeed undesirable to introduce more than 20 to 25 cc. of air in all. Even this amount might be thought to be excessive, but, in nearly every case, some of the air escapes outside the ventricles. If, on the other hand, the ventricles are seen on the initial radiographs to be enlarged, it may be necessary to inject 70, 80, or even 100 cc. of air, being guided by serial

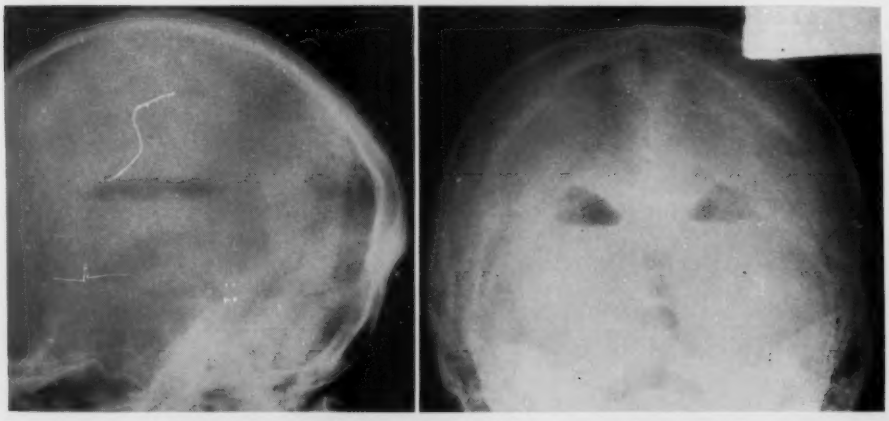


Fig. 5. [Left and right] Normal air encephalogram; 7 cc. of air injected

radiography as to the precise quantity required.

Clinical applications. The most important clinical application is in the diagnosis of cerebral atrophy, concerning which an enormous literature exists, but many of the problems are still unresolved. It is usually assumed that large ventricles indicate atrophy, but we cannot always be certain. We know, in fact, that sometimes an individual with very large ventricles may have a normal intelligence.

Over twenty years ago, Wartenberg[13] said: "Clinical evaluation of local or diffuse atrophy of the brain must be made with care. One is not entitled to judge immediately the mental capacity of the patient from the volume of the brain substance visible in the encephalogram. Pope Julius III is supposed to have said: It is unbelievable with how little wisdom the world is governed! Upon reviewing an encephalogram, it might be remarked: It is unbelieveable with how little brain substance one can get along in life! Again and again I have found, by encephalography, the brain substance to be greatly reduced in patients who showed no mental deterioration at all, or at least not to a commensurable degree. There is no strict parallelism between the volume of the brain and the mental capacity of the individual. The encephalographic method, valuable as it is, is too crude to serve as a gauge for the possible impairment of the mental state."

We should still heed these remarks and even amplify them to include some cases of hydrocephalus due to raised intracranial pressure. A striking example of the association of very large ventricles and normal intelligence is sometimes seen in aqueduct stenosis. Here, the lateral and third ventricles are nearly always enormously enlarged and must have a capacity of several hundred cubic centimeters. Indeed, they may be so large that their combined capacity is perhaps greater than the residual, greatly compressed, supratentorial portion of the brain. Nevertheless, intelligence may be unimpaired and within normal limits. Many examples come to mind but one in particular may be quoted, the case of a boy aged 15. In May 1950, he complained of having had 2 falling attacks a few weeks previously. On one of these occasions, he thought he may have lost consciousness for a few seconds. Having been good and keen at games, he had recently become a little slow and thought also that his work had deteriorated somewhat. About two years previously, he had been almost up to scholarship standard. On examination, early bilateral papilledema was found and the circumference of the head was 23 in.; both temporal fossae were bulging slightly. He had no history of headaches. A diagnosis of tumor in the posterior fossa or in the region of the third ventricle was made. A tentative diagnosis of aqueduct stenosis was made on the plain roentgenograms, and positive contrast ventriculography was the next procedure undertaken. A very small quantity of air was also introduced at the same time. The diagnosis was confirmed, and Torkildsen's ventriculocisternostomy was performed. Some index of his mental capacity is given by the fact that at the time of operation he was at one of England's best schools and holding his own mentally with boys of his own age. Now, ten years later, he works on the London Stock Exchange, apparently quite successfully, and recent medical examination revealed no mental deterioration.

THE THIRD VENTRICLE

Attention must be drawn to this structure since the literature contains dogmatic statements regarding the significance of its maximum width. If it is well filled with air, it is easily defined in anteroposterior projection and its greatest width is readily measured. Last and Tompsett recorded the maximum width of the third ventricle in their 24 casts and found that it varied between 4 and 11 mm., the average being 5.5 mm.; 8 of these ventricles had a maximum width of as much as 6 mm., and only 1 of them was from a ventricular system of over 30 cc. total capacity. Therefore, if one accepts 30 cc. as the upper limit of normal for the capacity of the ventricular system (and this limit may be too strict), one must accept 6 mm. as a normal width for the third ventricle. The lateral walls of this ventricle are formed by the thalami. It is known that these structures vary in length, and there seems no reason why they should not also vary slightly in width and yet remain normal.

It is important to mention these points,

particularly in order to discourage possible unfounded conclusions regarding cerebral atrophy. For example, it has been stated by so great an authority as Lindgren[14] that a third ventricle with a width of over 3 mm. is abnormal and is a sign of atrophy.

CONCLUSIONS

Modern anatomic findings indicate that the average normal ventricular system has a capacity of less than 20 cc., probably about 16 cc. There would apepar to be no minimum limit, but, in practice, about 7 cc. is the smallest volume. It is much more difficult to define the upper limit of normal, but anything in excess of 30 cc. might reasonably be treated with suspicion, though Last and Tompsett had one brain with a ventricular capacity of over 56 cc. which they considered to be normal.

Practical applications of these findings inevitably follow in the performance of air encephalography. Methods of measuring ventricular volumes in life have been discussed. Any possible correlation between ventricular volume and the appearances of the cerebral cortex has not been considered.

The author is greatly indebted to Professor Last and Dr. Tompsett for access to their material and for permission to radiograph their specimens. He is also grateful to Professor Knudsen for permission to reproduce Figure 1.

REFERENCES

1. Wartenberg, R.: Robert Wartenberg, the neurologist. J. Nerv. & Ment. Dis. 116:484, 1952.
2. Bruijn, G. W.: Pneumoencephalography in the Diagnosis of Cerebral Atrophy. Utrecht, H. J. Smits, 1959.
3. Welcker, H.: Zwei Hülfsmittel bei Demonstration des Gehirns und des Herzens. Virchows Arch. f. path. Anat. 74:500, 1878.
4. Retzius, G.: Cited by Last and Tompsett.[8]
5. Harvey, R. W.: The volumes of the ventricles of the brain. Anat. Rec. 5:301, 1911.
6. Brück, C.: Das Ventrickelsystem des menschlichen Gehirns. J. f. Psychol. u. Neurol. 45:545, 1934.
7. Morel, F., and de Montmollin, R.: Ventriculométrie; de la capacité des ventricules cérébraux et de ses modifications. Monatschr. f. Psychiat. u. Neurol. 104:1, 1941.
8. Last, R. J., and Tompsett, D. H.: Casts of cerebral ventricles. Brit. J. Surg. 40:525, 1953.
9. Knudsen, P. A.: Ventriklernes Storrelsesforhold i Anatomisk Normale Hjerner fra Voksne Mennesker. Odense, Andelsbogtrykkeriet, 1958.
10. Tompsett, D. H.: Personal communication, 1959.
11. Evans, W. A.: Encephalographic ratio for estimating ventricular enlargement and cerebral atrophy. Arch. Neurol. & Psychiat. 47:931, 1942.
12. Robertson, E. G.: Encephalography. Melbourne, The Macmillan Co., 1941.
13. Wartenberg, R.: Experiences in use of encephalography. J. Nerv. & Ment. Dis. 89:640, 1939.
14. Larsby, H., and Lindgren, E.: Encephalographic examinations of 125 institutional epileptics. Acta psychiat. et neurol. 15:337, 1940.

Angiographic appearances in acute intracranial hypertension

H. F. W. Pribram, D.M.R.D.

INCREASING INTEREST in the etiology of cerebrovascular accidents such as subarachnoid hemorrhage and carotid thrombosis has resulted in the more frequent and earlier recourse to angiography as a diagnostic aid. In the past eighteen months, a number of cases of proved subarachnoid hemorrhage have been encountered in which, at angiography, there was narrowing of the internal carotid artery in the neck and failure to demonstrate the intracranial vessels.

In each case, a good puncture had been made and, although there was excellent filling of the external carotid circulation, the contrast medium remained in the internal carotid artery, reaching no further than the base of the skull or the upper limits of the carotid syphon. Repeated injections were made, and films with up to nine seconds delay were taken. These showed apparent obliteration of the lumen of the cervical portion of the internal carotid artery. The appearances resembled those of carotid thrombosis, yet there was no evidence of collateral circulation and postmortem examination failed to disclose any anatomic obstruction. The appearances might therefore be attributed to arterial spasm.

It was decided to investigate such cases in order to determine whether the appearances were in fact due to spasm, if anything could be done to overcome the apparent obstruction, and whether any particular significance lay in the appearances.

In all, 17 patients were examined, but the report is confined to 10, as postmortem confirmation is lacking for 4 and the remaining 3 would not have contributed anything of interest.

A high percentage of cases of intraventricular hemorrhage was found, and the reason for this will be discussed later. A case of confirmed carotid thrombosis is included in the series on account of the similarity of the angiographic appearances.

CASE REPORTS

Case 1. The study commenced with Clare T., a married woman of 25, who was admitted to the Central Middlesex Hospital under the care of Dr. R. Asher on August 15, 1958, as having subarachnoid hemorrhage.

She rose at about 6:30 A.M. on that morning and went to the bathroom. Shortly after, she was heard to cry out: "I am very sick, John." Since that moment, she had remained unrousable. Before that time, she had been in good health and was thought to be about sixteen weeks pregnant.

On admission at 7:15 A.M., she was unconscious with stertorous breathing. Her pulse was regular at 80; her blood pressure was 140/75. She made occasional spontaneous movements with her right arm. The pupils were fixed and dilated. The fundi were pale, and a number of subhyaloid hemorrhages were noted. The right arm and leg were spastic, the left flaccid. All reflexes were brisk, those on the right more than those on the left; both plantars were extensor.

At 10:15 A.M., she had a tonic convulsion and became cyanosed. Respirations became poor and then ceased. Artificial respiration was commenced. Lumbar puncture showed uniformly bloodstained cerebrospinal fluid with a pressure of 200 mm. Arteriography was performed at 4:15 P.M.

The right carotid artery was noted to pulsate poorly but not otherwise abnormally. After injection, only about 4½ cm. of the internal carotid artery filled; thereafter, it was seen to terminate as a slender filament at the upper border of C2. Excellent filling of the external carotid circulation was obtained. Late films showed no progress of the contrast medium, no intracranial filling, and no evidence of collateral circulation. A film of the neck showed contrast proximal to the needle, which was in good position.

The left carotid artery pulsated equally poorly. Compression of it resulted in neither cardiac arrest

From the Central Middlesex Hospital, London, and the Department of Radiology, University Hospital, Edmonton, Alberta, Canada.

nor irregularity. Films of this side were identical with those of the right side.

The patient died at 5:30 A.M., August 17.

Postmortem arteriography showed all vessels to be patent. An angiomatous malformation within the right lateral ventricle was demonstrated. The ventricular system was tensely distended with blood, and a small angioma was identified within the blood clot in the right lateral ventricle. The convolutions were flattened, and there was clotted blood in the subarachnoid space.

Comment. It was concluded that the occlusion of the internal carotid artery in the neck could have been due to an obliterative spasm severe enough to arrest the blood flow completely. It was thought that such spasm might occur in cases of intraventricular hemorrhage in the same way as spasm is seen in intracerebral vessels in the proximity of an aneurysm. An attempt was made to study further cases.

Case 2. Rhoda K., aged 28, was admitted on March 14, 1958, to the care of Dr. Rowland Hill at the West End Hospital for Neurology and Neurosurgery. She was conscious, and no abnormal physical findings were recorded. The patient, who had previously been in good health, was walking home seventeen days before admission when she suddenly found she could neither see nor hear properly. Her legs would not move when she tried to walk, although she was standing upright holding on to a fence. Five to ten minutes later, she had a very severe headache and began to vomit repeatedly.

She was admitted to the local hospital and remembered arriving there, but the next five days remained a blank. The headache lasted for about a week and then recurred only in the evenings.

At 5:30 P.M. March 16, she was about to wash herself when she suddenly vomited and lost consciousness. On examination, she was semiconscious and incontinent of urine. The left arm was at first flaccid and then became extremely spastic. The right arm and both legs were hypertonic. Reflexes were increased in the right arm but equal elsewhere. Plantars were not obtainable.

The pupils were constricted but reactive. There was no neck stiffness. Blood pressure was 150/100 and pulse 58.

At 5:45 P.M., the pupils dilated and became unreactive and irregular. Papilledema on the left and fresh hemorrhages on the right were noted. Coma became deeper. At 6:15 P.M., she became completely flaccid with hyperreflexia of all limbs. At 7 P.M., spontaneous respiration ceased and artificial respiration was commenced.

At 9:30 P.M., she had widely dilated, fixed pupils. Hemorrhages were present in both fundi. All limbs were flaccid and all reflexes absent. Blood pressure was now 90/60. Arteriography was then performed.

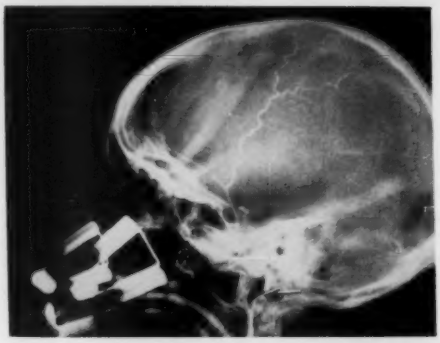


Fig. 1. Carotid arteriogram *(Case 2)* in case of intraventricular hemorrhage from aneurysm situated at bifurcation of left internal carotid artery. Dye column narrows to a "rat-tail" at upper border of C1 and then broadens again. If film is held in position in which it was taken, the appearances resemble a "waterfall," with dye clinging to the most dependant part of the vessel—the result of exceedingly slow blood flow.

The right internal carotid artery was punctured, and serial films showed the needle to be in good position. The external carotid circulation was normal. The internal carotid artery showed features that were almost identical to those encountered in the first case. The internal carotid artery became a slender ribbon at the upper border of C1. It then dilated so that contrast filled the beginnings of the carotid canal. No intracerebral filling was obtained (Fig. 1). The patient died before arteriography on the other side could be performed.

Autopsy showed little in the way of an uncal pressure cone. A large hematoma was disclosed in the left frontal region originating from an aneurysmal sac, the size of a currant, situated at the junction of the anterior and middle cerebral arteries. The aneurysm faced forward and laterally. The ventricular system was distended with blood. The brain stem was normal.

Comment. This case with contrast proximal to the needle point and the internal carotid artery constricted to the size of a slender ribbon in the upper neck and then dilating to normal size in the carotid syphon would therefore *appear* to satisfy all criteria of an obliterative spasm secondary to intraventricular hemorrhage. It should be noted that there was no evidence of uncal or tonsillar herniation nor of brain stem hemorrhage.

Case 3. Dr. Robert S., aged 28 and on holiday in Rome, returned from a party at 4 A.M. on

October 7, 1958, with a pain in the left temple that radiated into the left eye and down into the neck whenever he coughed, strained, or moved. He awoke in the morning with a headache and expressive aphasia. He understood what was said and knew what he wished to say but could express himself neither verbally nor in writing. He had particular difficulty with the names of certain objects and places. He had no dysarthria or neck stiffness.

The next day, he had an attack of numbness and tingling on the right side of his face and body which lasted for about ten seconds and never recurred. The day after, he consulted a neurologist who found his blood pressure to be raised to the order of 160/100.

On inquiry, it appeared that, when he was 16, a systolic murmur maximal in the pulmonary area and radiating to the apex as well as a raised blood pressure had first been observed. He was not investigated, and no restriction was placed on his athletic activities.

He was admitted to the National Hospital for Nervous Diseases, Queen Square, under the care of Dr. J. Marshall on October 10. Examination showed no neck stiffness or dysarthria. Expressive aphasia and partial right homonomous hemianopsia were recorded. In addition, he had slight right facial and right-sided weakness.

A harsh systolic murmur in the pulmonary area that radiated into the neck and to the apex was heard. His blood pressure was 160/100, and the peripheral pulses were normal. Skull and chest roentgenograms were also normal. The cerebrospinal fluid was clear.

At 10:30 A.M. October 16, he was found unconscious and cyanosed. The pupils were fixed and dilated; all 4 limbs were flaccid and hypotonic. The cerebrospinal fluid was heavily bloodstained.

Bilateral arteriography was performed under positive pressure respiration.

Puncture of the left common carotid artery resulted in filling of both the external and internal carotid artery circulation. The internal carotid artery was seen to end as a "rat-tail" at the level of C1, beyond which only meager filling was obtained.

Puncture of the right common carotid artery resulted in good filling of the internal carotid artery. The artery "narrowed" in the upper cervical region, but some contrast entered the carotid syphon (Fig. 2). On both sides, contrast was present proximal to the needle point. In all respects, appearances were identical to those noted in the other two cases. Both punctures were beyond reproach.

Postmortem examination showed a saccular, wide-based aneurysm arising from the right middle cerebral artery which had bled into the hemisphere and the ventricle as well as into the subarachnoid space. In addition, coarctation of the aorta was noted distal to the left subclavian artery. The diameter of the stenotic area measured 2.6 cm.; a patent ductus arteriosus was present.

Fig. 2. Carotid arteriogram *(Case 3)* in case of intraventricular hemorrhage from right middle cerebral artery aneurysm. Narrowing of internal carotid artery resembles the appearances of carotid artery thrombosis, as in Figure 4.

Comment. Since all the patients reported on so far had angiography performed while being maintained by artificial respiration, it was of some interest to see whether the appearances might be due to this cause alone or due to the fact they were moribund. In this respect, the following case is relevant.

Case 4. John S., aged 49, collapsed in the street at 11:15 A.M. on December 26, 1957. He remained unconscious for about ten minutes but was able to get home. He complained of very severe headache, vomited, and lay down. At 2:30 P.M., he was found unconscious with Cheyne-Stokes respiration, fixed, dilated pupils, and flaccid limbs.

On admission to the Oldchurch Hospital under the care of Mr. K. Paine, he was deeply unconscious and his pupils were fixed and dilated; there was no neck stiffness. All limbs were flaccid, and the plantar responses could not be obtained. His blood pressure was 180/90. Before admission, while he was at another hospital, extensor rigidity of all limbs and bilateral extensor plantar responses had been noted.

Inquiry from relatives revealed that, two years previously, he had sustained a head injury with a depressed fracture that had to be elevated.

Bilateral carotid arteriography was performed.

Puncture of the left common carotid artery

resulted in good filling of the external and internal carotid circulations. The internal carotid artery terminated at the upper level of C1; some contrast entered the carotid syphon, which appeared to be of normal caliber. The right internal carotid artery showed similar appearances, but better filling of the syphon was obtained. The needle on each occasion was in good position.

Autopsy showed intraventricular hemorrhage from a left anterior communicating artery aneurysm.

Comment. This, then, was the first case in which artificial respiration could be eliminated as a causative factor. It is noteworthy that the appearances were identical in all the cases and that, where the carotid syphon was filled, its caliber was normal and there was no evidence of any spasm within it. This point will be discussed further.

Case 5. Ursel C. aged 41, a visitor from the United States, was out shopping with his wife on January 17, 1959, when he complained of severe pain in the occipital region which progressed to a generalized headache in both frontal regions. He had no nausea or diplopia and did not vomit. A general practitioner found no abnormality.

At 8:30 A.M. January 27, he went to the toilet and collapsed, falling forward and complaining of severe headache in the left temple. He vomited. He stated that there had been a "pop" in his left temple.

On examination at 10 A.M., the only recorded abnormalities were right hemiparesis and a pulse rate of 48; he was vomiting. Lumbar puncture showed a grossly bloodstained cerebrospinal fluid at a pressure of over 300 mm.

At 11:30 A.M., he became unconscious and his breathing was stertorous. He was then transferred to the National Hospital for Nervous Diseases under the care of Dr. J. Marshall.

On admission he was comatose, pale, and ill. His head and eyes were turned to the right. He made no response to painful stimuli. His pupils were unreactive; the left was ovoid and 3 times the size of the right, which was small and circular. The fundi were normal. The blood pressure was 180/150 and later fell to 140/90. (He had been a known hypertensive for some years with a blood pressure 25% above normal; he had also had severe headaches for about a year).

Extensor spasms were frequent. His left hand made purposeful movements; the right was not used. The reflexes varied with the tone and were either very brisk or sluggish. The plantars were unresponsive.

Right carotid arteriography was performed and showed very marked narrowing of the upper cervical portion of the internal carotid artery with some filling of the syphon. The appearances were identical with those already described (Fig. 3).

He died at 9:30 P.M. Autopsy was not performed.

Fig. 3. Carotid arteriogram *(Case 5)* in case of subarachnoid hemorrhage due to possible right middle cerebral artery aneurysm. Note resemblance to the appearances in the case of carotid artery thrombosis in Figure 4.

Comment. At this stage, it became of some importance to find a case in which the same appearances were obtained at arteriography and in which the patient was neither moribund nor being artificially respired. The next case satisfied these conditions.

Case 6. Harold B., aged 42, was admitted to the Atkinson Morley Hospital under the care of Mr. Wylie McKissock on January 26, 1956. Just before Christmas 1955, he had a severe headache that lasted for about a fortnight. Since then, he had had occipital headaches.

Eight days before admission, he became giddy, vomited, and had severe occipital headaches. At first, he was treated at home and then transferred to hospital.

On admission, he was drowsy. Marked neck stiffness and photophobia were noted. The pupils were small but reacted normally. His blood pressure was 150/100. No other abnormal physical findings were recorded. Lumbar puncture showed uniformly bloodstained fluid at a pressure of 270 mm.

Arteriography of the left common carotid artery showed the internal carotid to taper and finally end as a slender filament 1½ in. above the bifurcation. The right carotid artery was punctured the next day, and a small angioma situated in the region of the right choroid plexus was demonstrated. Drainage was by a large basal vein. Some

displacement of the anterior cerebral artery to the left was noted.

Surgery was thought inadvisable as a severe neurologic defect was likely to follow. He was discharged from hospital but had a further bleed on February 16, 1957. When last heard of on April 24, 1957, he was alive and in good health.

Comment. The arteriographic appearances were identical to those previously observed, and, as in all the other cases, the position of the needle within the artery was beyond reproach, so that the spasm could not have been due to a faulty injection as described by Decker.[1] Neither a moribund condition nor artificial respiration could be the causative factor in this case, which would appear to confirm the view that intraventricular blood might be a causative factor. At this stage of the investigation, I was reminded of a most unusual case.

Case 7. June D., aged 26, was admitted to the National Hospital for Nervous Diseases, Queen Square, on April 23, 1958, under the care of Mr. Wylie McKissock. One week before admission, she had had a stiff neck, and, the day previous, she had had a very severe headache and gone to bed. On the day of admission, she complained of a "filthy" headache, vomited 3 or 4 times, and, at midday, collapsed unconscious.

She had suffered with migraine for some years and had had attacks of headache in the frontal and parietal regions since the age of 8 or 9. In the last four years, the headaches had become worse and she saw shimmering lights and had attacks of giddiness and loss of vision.

On admission, she could state her name but spoke with slurred speech; she responded to painful stimuli. Marked neck stiffness, conjugate deviation of the eyes to the right, and right-sided ptosis with a right third nerve palsy were noted. The left pupil was larger than the right. A left homonomous hemianopsia was thought to be present. In addition, there were left fifth and seventh nerve palsies.

The left arm was flaccid and paralyzed; the right arm was hypotonic, but power appeared normal. Similar findings were present in the legs. Reflexes were equal and both plantars extensor. Blood pressure was 165/110. Lumbar puncture confirmed subarachnoid hemorrhage.

A right carotid arteriogram showed the following appearances. The internal carotid artery was narrowed to a rat-tail over 2½ in. in the region of the third to the first cervical vertebra. Good external carotid filling was obtained. In late films, contrast could be seen up as far as the top of the carotid syphon, where it stopped abruptly.

She died the next day, and autopsy was performed.

Recent blood was present in the interpeduncular cistern as well as on the orbital surface of the right frontal lobe. Both hemispheres were swollen, the right more than the left. Within the right frontal horn was an ovoid recent blood clot measuring 30 × 10 mm. enclosed in a smooth, soft membrane. This was attached to the floor of the ventricle by a thrombosed vessel leading to the basal arteries. Recent antemortem, reddish, adherent thrombus was present in the internal carotid artery from just beyond the origin of the ophthalmic artery and also in the right anterior and middle cerebral arteries. No anterior communicating artery was found. Hemorrhagic infarction was present along the distribution of the right middle cerebral artery. The pathologist felt that the source of bleeding had been an intraventricular angioma and that this had been the start of the retrograde thrombosis.

Comment. It seems extremely likely that, in this case, there was extreme slowing of circulation in the internal carotid artery as already observed in the other cases and that this allowed the thrombosis to occur. This complication was not observed in the other patients, probably because they did not survive long enough for it to take place.

Appearances similar to those above have been described in cases of primary carotid thrombosis by Murphey and Shillito,[2] and it is now pertinent to consider such a case.

Case 8. Albert G., aged 43, was admitted on December 15, 1954, to the care of Mr. T. G. I. James at the Central Middlesex Hospital. On December 2, he had collapsed while at work in a steel mill. On examination, he had been conscious but lethargic, drowsy, and disinclined to answer questions. He had been a known hypertensive for a number of years. Six hours before admission, he had awakened during the night with some generalized headache but had gone back to sleep. He was quite well in the morning and went to work as usual but collapsed soon after starting work. On examination, some weakness of the right side of the face and right hemiplegia were recorded. His blood pressure was 165/95. Lumbar puncture revealed a clear, colorless fluid.

He remained drowsy for a day or two with no alteration in the neurologic signs. On the ninth day, he had a generalized epileptic fit, followed the next day by 4 further fits. On December 15, early papilledema was thought to be present. An electroencephalogram was thought to be compatible with a lesion in the left centroparietal region, and an angiogram was requested. The left common carotid artery was punctured; the proximal half inch of the internal carotid artery was normal in diameter, but the vessel above this narrowed rapidly and was constricted for at least 2 in. The circulation was extremely slow, and filling was ob-

tained only up to the level of the top of the carotid syphon. No filling of the intracerebral vessels was obtained (Fig. 4).

The right common carotid artery was punctured and showed good filling of the internal carotid artery and both anterior cerebral arteries. The main stem of the left anterior cerebral artery was filled back as far as the origin of the vessel.

On January 18, 1956, the left common carotid artery was explored. At operation, an atheromatous plaque was found on the common carotid artery, starting three-quarters of an inch below the bifurcation and extending up to the bifurcation and then up the internal carotid artery. Pulsation was noted in the internal carotid artery, and the appearances on the angiogram were thus presumed to be due to the atheromatous plaque.

After the operation, a surprising amount of recovery occurred in the movement of the right arm, and, at discharge on February 10, 1956, power in the right leg was normal.

Comment. The points of interest in this case are that, while the angiographic appearances resembled those of the other cases, lumbar puncture had shown a clear cerebrospinal fluid and the angiogram had shown evidence of collateral circulation.

Until now, only cases that conformed to certain standard appearances—tapering of the contrast column in the upper cervical region and absence of any evidence of spasm within the carotid syphon or of the intracranial portion of the internal carotid artery—had been considered because it was believed that the narrowing of the dye column was due to spasm and that there was something specific about the appearances of the internal carotid artery in cases of intraventricular hemorrhage. The realization now came, after a close study of the film, that the appearances were fortuitous. They could be explained on the basis of "streaming" or "layering," and there was no reason to believe that they were due to spasm.

Accordingly, the net was cast wider to see whether these appearances were specific for intraventricular hemorrhage. The following 2 patients had no evidence of intraventricular hemorrhage but showed similar angiographic findings.

Fig. 4. Carotid arteriogram *(Case 8)* in case of almost complete occlusion of internal carotid artery by arteriosclerotic plaque.

Case 9. Doris C., aged 51, was admitted to the Atkinson Morley Hospital, on December 16, 1958, to the care of Mr. Wylie McKissock. On admission, she was stuperose and inaccessible. She was restless and made groping movements with her upper limbs. The pupils were fixed and dilated. Blood pressure was 170/60. Lumbar puncture revealed uniformly bloodstained fluid. The only history obtainable was that she had had severe headache and had vomited the previous night.

Left carotid angiography was performed with the patient in a respirator. Filling of only the proximal few centimeters of the anterior and middle cerebral arteries was obtained.

The patient died, and autopsy showed gross flattening of the cerebral convolutions. There was blood in the left sylvian fissure from a ruptured middle cerebral artery aneurysm; this had bled into the frontal lobe, leaving a huge cavity. No evidence of intraventricular bleeding was found.

Case 10. Catherine W., aged 49, was admitted unconscious to the University of Alberta Hospital under the care of Dr. F. Donald on October 23, 1959. The past history was of pain in the back of the neck for about eighteen months. The recent history was that, at 9:30 P.M. on the day of admission, she suddenly fell to the ground unconscious. On admission, both pupils were widely dilated, breathing was stertorous, and she was deeply unconscious. Lumbar puncture showed bloodstained fluid under a pressure of 250 mm. Bilateral carotid angiography was performed, and, although there was good filling of the external

carotid circulation, the contrast medium only reached as far as the top of the carotid syphon (Fig. 5). The appearances were almost identical with those of Case 7.

The patient died at 12:30 A.M., two and one-half hours after admission. Autopsy showed a ruptured aneurysm at the site of origin of the right posterior communicating artery. A massive subdural hemorrhage and some subarachnoid blood were found. Pressure cones were prominent on the cerebellar tonsils. A recent hemorrhage was seen in the pons.

Comment. A point still required elucidation: Was there any way of demonstrating the intracerebral circulation in cases such as we have considered above? Papaverine, whether intra- or periarterial, has been disappointing in overcoming arterial spasm, and, in any case, it was now by no means certain that the appearances were due to spasm. Riishede and Ethelberg[3] used papaverine in their cases and reported similar appearances. Browne and Stern[4] reported that stellate ganglion block did not prevent the occurrence of spasm in the carotid artery of the cat. Horwitz and Dunsmore[5] performed a stellate ganglion block before angiography in one of their cases. In the present series, all are cases of acutely raised intracranial pressure. If the appearances are related to this, it follows that, if the pressure is relieved, filling of the intracerebral circulation will result. The time eventually came when the thesis could be tested.

Fig. 5. Carotid arteriogram *(Case 10)* in case of subdural and subarachnoid hemorrhage from right posterior communicating artery aneurysm. The appearances at top of carotid syphon might be mistaken for those of carotid artery thrombosis at bifurcation, as in Case 7.

Case 11. Mrs. Elizabeth H., age 22, was admitted to the University of Alberta Hospital under care of Dr. G. Monckton on December 30, 1959. She was being maintained under artificial respiration.

She had attended as an outpatient two weeks before Christmas with a year's history of attacks of paresthesias in the right arm and leg as well as attacks of dysphasia. These had become more frequent of late. Neurologic examination was essentially negative, but she was found to be about thirty-two weeks pregnant. Admission for investigation was advised, but, as it was so close to Christmas, she was unwilling to come into hospital.

At 11 A.M. on the day of admission, she had an epileptiform convulsion and had remained unconscious ever since. At 2 P.M., she had a further series of right-sided fits and spontaneous respiration ceased. Mouth-to-mouth respiration was begun and continued until arrival in hospital at about 3:30 P.M., when an endotracheal tube was passed.

On examination, she was completely unconscious. The right pupil was larger than the left, and neither reacted to light. The fundi were normal, and there was no evidence of papilledema or hemorrhages. No bruit was noted. No fetal heart sounds were heard. Lumbar puncture showed uniformly bloodstained fluid under considerable pressure. The blood pressure was about 50.

Carotid pulsation was feeble, but the left common carotid artery was punctured with ease. After injection, good filling of the external carotid circulation was obtained but the contrast medium remained in the internal carotid artery and did not reach beyond the limits of the carotid syphon. As previously noted, the contrast column narrowed in the upper cervical region and then broadened as it reached the carotid syphon. Delayed films showed no progress of the contrast column (Fig. 6). The needle was left in position, and, meanwhile, a twist drill burr hole was made in the right parietal area. The right lateral ventricle was encountered in normal position, and xanthochromic, bloodstained cerebrospinal fluid under greatly increased pressure was obtained. The blood pressure remained in the region of 50 to 60.

Immediately after, the angiogram was repeated and good filling of the intracerebral vessels was obtained. The pericallosal artery was stretched, indicating the presence of an appreciable amount of hydrocephalus. A large, angiomatous malformation lying deep in the posterior temporal region and supplied by the middle cerebral and anterior

Fig. 6. Carotid arteriogram *(Case 11)* in case of intraventricular hemorrhage from a choroid plexus angioma. No filling of the intracranial vessels is shown.

Fig. 7. Carotid arteriogram *(Case 11)* immediately after ventricular puncture demonstrating the choroid plexus angioma and normal filling of the intracranial vessels.

choroidal arteries was outlined. Venous drainage was by a greatly enlarged thalamostriate vein, the internal cerebral vein, and the vein of Galen (Fig. 7).

The lesion was considered inoperable, and the patient died at 9:30 P.M.

Postmortem examination showed flattening of the convolutions with marked pressure cones on the uncus and cerebellar tonsils. The third nerve was flattened. The fourth ventricle, aqueduct, and third and lateral ventricles were tensely distended with blood. An angiomatous malformation within the left lateral ventricle was identified in the region of the trigone.

DISCUSSION

Constriction of a vessel proximal or distal to an intracranial aneurysm that has bled is a commonplace finding at arteriography. Such constriction may vary in degree and may persist for two or three weeks after subarachnoid hemorrhage. It may even be severe enough to prevent the aneurysm from being demonstrated.

Such appearances are probably due to spasm, since they may be present at one examination and absent at another or at autopsy. The narrowing may persist for some time and result in slowing of the circulation, so that spontaneous clotting in the aneurysm and its parent vessel may follow.

It might therefore be thought that the failure to demonstrate the intracerebral vessels in the above cases could be attributed to spasm in the cervical portion of the internal carotid artery. This belief is encouraged by consideration of the films obtained in Case 2, where the dye column is seen to narrow to a slender filament at the upper border of C1 and then to broaden out again at the base of the skull (Fig. 1).

Late films showed little or no advance of the dye column, but its failure to ascend beyond the limits of the carotid syphon is not explicable on the basis of spasm as no radiologic evidence of it was found at this level. The arrest of the dye column at the carotid syphon may, however, create a false impression of arterial occlusion, as in Case 10 (Fig. 5).

The similarity in appearances to cases of genuine carotid occlusion is of interest because one may be mistaken for the other. Thrombosis of the internal carotid artery begins shortly above the bifurcation, and the narrowing of an arteriosclerotic carotid artery to almost complete occlusion (as in Case 8) bears marked similarity to the cases under discussion (Fig. 4). Once thrombosis has occurred, a slender filament can often be demonstrated curving its way up to the base of the skull. The relationship of the above cases to those of genuine carotid occlusion is best illustrated by

Case 7. It seems reasonable to suppose that, after the intraventricular hemorrhage, the circulation was slowed so much that clotting took place in the distal vessels.

The internal carotid artery in this case tapered as in the others, but the contrast finally stopped abruptly at the top of the syphon at a point subsequently shown to be the site of thrombosis.

The possibility of false localization of the site of thrombosis has been stressed by Murphey and Shillito,[2] who reported a narrowed contrast column in the internal carotid artery proximal to the true site of thrombosis. They presented 4 cases, of which 2 were confirmed by autopsy and 1 by operation. They stress the importance of taking late films for correct localization. It will be seen from the present series that, even then, the distinction may not always be possible. It is felt, therefore, that, before a diagnosis of carotid thrombosis is made, some evidence of collateral circulation must be found.

Spasm of the internal carotid artery is known to occur but is usually provoked by trauma in one form or another. Browne and Stern[4] showed experimentally that both diffuse and focal spasm could occur in the extracranial carotid artery of the cat.

Ecker[6] described 4 cases in which injury in the neck was thought to have led to spasm in the internal carotid artery. However, no angiographic confirmation was offered. Ecker and Riemenschneider,[7] in a full discussion on arterial spasm, limit themselves to a consideration of the intracranial portion of the internal carotid artery. They state that the stimulus for spasm may be traction, the occurrence of embolism, or the application of an artery clip. Touching the internal carotid artery in its subarachnoid course may also provoke spasm.

Decker[1] reported spasm in the internal carotid artery, but, in all his cases, this was due to a faulty injection of contrast medium. It was, however, noticeable that his cases show a zone of narrowing in the internal carotid artery yet, nevertheless, good filling of the intracranial vessels. In other words, spasm did not obliterate the vessel lumen completely. His cases are not relevant to the discussion, as, in the present series, the needle was seen to be in good position.

In a symposium on arterial spasm in subarachnoid hemorrhage, Johnson, Potter, and Reid[8] specifically state that such spasm is confined to the intradural vessels. They add that only vessels in the neighborhood of the carotid syphon are affected and that distal vessels are unaffected. They believe that mechanical factors are responsible and that spasm may occur with severe subarachnoid bleeding unassociated with any intracerebral hemorrhage. They also suggest that the appearance of narrowing may be produced by changes in blood flow.

If the films referred to earlier (Fig. 1) are studied in the position they were taken, it becomes obvious that a different interpretation of the findings is possible. It is what I should like to call a "waterfall effect." The dye column moves slowly to the upper border of C1 and then "falls" into the beginnings of the carotid canal situated more posteriorly; the dye clings to the most dependent portion of the vessel. Thus, there is no need to assume the existence of spasm as the appearances can be explained solely on the basis of an extremely slow circulation.

Other authors have reported failure to demonstrate the intracranial vessels at angiography. Riishede and Ethelberg[3] reported 5 cases, 2 of which were cases of intraventricular hemorrhage. They attribute the appearance to "sudden and severe herniation of the brain stem through the tentorial incisura." One of their patients improved after ventriculography, and a repeat angiogram performed three days later outlined a bifrontal glioma.

In a discussion on the cause of the angiographic appearances, the authors state that they believe it is unreasonable to suppose that the lumen of the carotid artery could be completely obliterated by spasm. They reinforce this argument by stating that there is no evidence of spasm in the external carotid artery. They consider it unlikely that the changes are due to direct compression of the vessels, as this would then have to include the basilar artery and this would shortly have resulted in death. A similar argument may be advanced for an explanation on a purely hydrostatic basis. They conclude that the changes are due to a change in blood flow mediated through the midbrain.

Horwitz and Dunsmore[5] reported 4 cases, but only 2 of these were confirmed at autopsy.

In 1, the fourth ventricle was filled with blood, the hemorrhage having originated in the hippocampal region. The other case was that of a ruptured right posterior communicating artery aneurysm. A ventriculogram had preceded the angiograms, but the air was not released.

They conclude that, in all their cases, a rise in intracranial pressure had occurred precipitously and that the failure to demonstrate the intracranial vessels could be due to a decrease in blood flow. One of their patients had a bony defect over the carotid canal, and they thought it possible that the artery might have been compressed directly.

Ryder and associates[9] stress the close relationship between the intracranial pressure and the cerebral blood flow, which in turn is influenced by the arterial blood pressure and the cardiac output. If the intracranial pressure is raised, the pressure is maintained providing the cardiac output remains constant. If the intracranial pressure goes on rising to equal the mean arterial pressure—about 1,300 mm. of water—a sudden rise in blood pressure and cardiac output takes place.[10] The authors go on to state that the rate of cerebral blood flow is as important as the volume of a space-occupying lesion in maintaining an elevated intracranial pressure. They conclude that reflex effects more powerful than anoxia and hypercapnia influence the intracranial pressure through the cerebral blood flow.

It should be noted that all the experiments were made on patients who had no obstruction to the intraventricular pathways, whereas the subjects we are considering did have such obstructions. It seems likely, therefore, that, in the present series, the angiographic appearances are due to a grossly diminished blood flow as a result of obstruction of the intraventricular pathways. Support for this hypothesis would come from the last case in the series, in which, before ventricular puncture, the blood flow was seen to be very slow in that films with up to nine seconds delay showed only a slight advance in the contrast column, whereas, immediately after tapping of the right lateral ventricle, the rate of flow appeared normal. The second series of films were taken at the normal interval.

No evidence of any residual spasm was seen. The left lateral ventricle still contained blood, thus invalidating the earlier idea that the mere presence of blood in the ventricle might provoke spasm of the extracranial internal carotid artery. At autopsy, blood clot distending the aqueduct and pressure cones at the uncus and cerebellar tonsils were present.

The high percentage of cases of intraventricular hemorrhage in the series is probably explained by the fact that the aqueduct becomes blocked with blood, thus precipitating acute hydrocephalus. In other cases, tentorial herniation takes place first and aqueduct obstruction later. In the 5 cases recorded by Riishede and Ethelberg,[3] 4 of the patients had obstruction of the intraventricular pathways.

Case 6 is of particular interest. On the day of admission, the intracranial vessels failed to fill at angiography. However, by the following day, the patient had recovered sufficiently for a good demonstration of the intracranial vessels to be achieved. It seems likely that there had been at least temporary obstruction of the intraventricular pathways and that this had resulted in a decrease in cerebral blood flow.

In future cases of alleged subarachnoid hemorrhage in which there is no filling of the intracranial vessels despite a good puncture and no evidence of collateral circulation, the ventricles should be tapped immediately. This would establish the presence or absence of an anatomic obstruction of the vessels.

It may be argued that a preliminary lumbar puncture would resolve this difficulty. However, infarcted brain may result in some subarachnoid blood. In any case, it is doubtful whether patients believed to have acutely raised intracranial pressure should be so tested when their state is probably due to tentorial herniation.

CONCLUSION

A series of 17 cases is described in which, at angiography, narrowing of the internal carotid artery in the neck was found and the intracerebral vessels could not be demonstrated. In none of these cases was there any evidence of anatomic obstruction.

All were cases of subarachnoid hemorrhage in which the intracranial pressure had risen acutely, and the majority of the patients had had intraventricular bleeding. The similarity of the angiographic appearances to those of ca-

rotid occlusion is stressed, and the relevant diagnostic criteria are reviewed. The possibility of confusion in the diagnosis is illustrated by reference to a patient proved to have atheromatous changes in the internal carotid artery.

The likely causes of the findings are discussed, and it is concluded that they are the result of a grossly slowed cerebral circulation resulting from greatly increased intracranial pressure. It is felt that there is no evidence to suggest that the appearances are due to arterial spasm.

The opinion was formed that, if such a case were encountered and the lateral ventricles tapped, filling of the intracerebral vessels would result. It was possible to test this hypothesis in a patient, a woman of 22 who had suffered a coma-producing subarachnoid hemorrhage. The left common carotid artery was punctured, but the contrast column never reached beyond the carotid syphon, even though films with up to nine seconds delay were taken.

With the carotid needle still in place, the right lateral ventricle was tapped and the angiogram repeated immediately with the ventricular needle still in situ. This time, there was good filling of the left internal carotid artery and its branches outlining a large choroid plexus angioma, the films being taken at the normal one-second interval.

It is recommended that, in future cases, the above course be adopted.

ADDENDUM

Since this paper was submitted, one further case of acutely raised intracranial pressure has been studied and on this occasion a vertebral arteriogram was performed.

Case 11. Barbara C., aged 2½, was admitted to the Royal Alexandra Hospital, Edmonton, under Dr. W. Yake at 6:45 P.M. on August 12, 1960. She was conscious and alert but mildly dehydrated. During the past month, she had been unusually irritable and difficult. She had vomited once at the onset of her illness. Two weeks before admission, she developed a right-sided squint, and for the last few days she had been listless and lethargic. She slept about fourteen hours a day and played little when awake.

At 10:30 P.M. the child had a series of tonic fits and went into coma. Her left pupil dilated and the right became constricted. At 2 A.M. she was completely unconscious with small inactive pupils.

Fig. 8. Left vertebral arteriogram (Case 11, see addendum) showing good filling of both vertebral arteries as well as the left posterior inferior cerebellar artery but no filling of the basilar artery. Note that the course of the proximal part of the left posterior inferior cerebellar artery is well below the foramen magnum thus showing evidence of tonsillar herniation. Note also the suture diastasis at the squamosal suture; diastasis was even more marked at the coronal suture.

She was in opisthotonus and had bilateral extensor plantar responses. Her pulse rate was 160. Lumbar puncture showed clear cerebrospinal fluid under increased pressure with a white cell count of 41 per cubic millimeter, the majority of these cells being polymorphs. A peripheral blood count showed 23,828 white cells per cubic millimeter, 82% of these being polymorphs.

At 4:15 A.M. all extremities were flaccid and no reflexes were elicited. Both pupils were dilated and bilateral papilledema was present. Her blood pressure was 142/70.

In view of the history of the left pupil dilating before the right, a left carotid arteriogram was attempted but the vertebral artery inadvertently punctured. The films showed good filling of both vertebral arteries as well as the left posterior inferior cerebellar artery but no filling of the basilar artery (Fig. 8).

The child died at 5:45 A.M. Autopsy showed an abscess in the left posterior temporal region; there was evidence of greatly increased intracranial pressure.

Comment. The appearances on vertebral angiography in cases of acutely raised intracranial pressure are thus seen to be exactly the same as those obtained at carotid angiography. The course of the posterior inferior cerebellar artery indicated tonsillar herniation while clear evidence of suture diastasis could be seen on the films. This confirms that, in cases of acute-

ly raised intracranial pressure, the cerebral circulation is slowed to such an extreme that death is inevitable without immediate ventricular puncture.

The author wishes to express his indebtedness to Dr. F. Pygott for his help and encouragement in the preparation of this paper and also to Dr. James Bull and Dr. G. F. Swann for assistance in securing cases for study. He is also grateful to the many physicians and surgeons who have allowed him to include cases that were in their care and thanks the Photographic Department of the National Hospital, Queen Square, London; the Central Middlesex Hospital, London; and the University Hospital, Edmonton, Alberta, Canada, for the reproduction of radiograms.

REFERENCES

1. Decker, K.: Der Spasmus der A. carotis interna. Acta radiol. 46:351, 1956.
2. Murphey, F., and Shillito, J.: Avoidance of false angiographic localization of the site of internal carotid occlusion. J. Neurosurg. 16:24, 1959.
3. Riishede, J., and Ethelberg, S.: Angiographic changes in sudden and severe herniation of the brain stem through the tentorial incisure. Arch. Neurol. & Psychiat. 70:399, 1953.
4. Browne, K. M., and Stern, W. E.: Experimental observations concerning cerebral angiography. Arch. Neurol. & Psychiat. 71:477, 1954.
5. Horwitz, N. H., and Dunsmore, R. H.: Some factors influencing the nonvisualization of the internal carotid artery by angiography. J. Neurosurg. 13:155, 1956.
6. Ecker, A. D.: Spasm of the internal carotid artery. J. Neurosurg. 2:479, 1945.
7. Ecker, A., and Riemenschneider, P. A.: Arteriographic demonstration of spasm of the intracranial arteries with special reference to saccular arterial aneurysms. J. Neurosurg. 8:660, 1951.
8. Johnson, R. J., Potter, J. M., and Reid, R. G.: Arterial spasm in subarachnoid haemorrhage. Mechanical considerations. J. Neurol., Neurosurg. & Psychiat. 21:68, 1958.
9. Ryder, H. W., Espey, F. F., Kristoff, F. V., and Evans, J. P.: Observations on the interrelationships of intracranial pressure and cerebral blood flow. J. Neurosurg. 8:46, 1951.
10. Evans, J. P., Espey, F. F., Kristoff, F. V., Kimbell, F. D., and Ryder, H. W.: Experimental and clinical observations on rising intracranial pressure. Arch. Surg. 63:107, 1951.

Oscillometry and pressure of the carotid artery

A preliminary report

S. Doğulu, M.D.

With the advent of carotid arteriography, occlusions of the common and internal carotid arteries have been diagnosed with increasing frequency. Unselected consecutive autopsies have shown complete occlusions of one or more vessels in 6.5% and severe narrowing in 3% of cases, indicating significant occlusive disease of the cervical carotid system.[1] The commonest site of occlusion is the carotid sinus, just at or beyond the bifurcation of the common carotid artery.

In spite of clinical features, the diagnosis of carotid artery occlusion always necessitates the use of objective methods: either angiography or ophthalmodynamometry. Although the results of angiography are very definite, it is not possible to apply this procedure to every case. Also, ophthalmodynamometry is an indirect method of diagnosis.

For the last six months, we have been conducting studies to determine how the pressure of the carotid artery, as measured by oscillometry, can be utilized in the early diagnosis of carotid artery occlusion. This is our first report on the subject.

Methods

The oscillometry of the carotid artery can be obtained with the modified cuff of a sensitive sphygmooscillometer. We used the Collens sphygmooscillometer. The cuff or collar prepared for this purpose is of flexible thin metal, coated with rather hard leather and lined with soft cloth. Two rubber balloons (6.5 x 12 cm.) are attached to the inner part. By means of 2 strips at the back, the collar can be fixed to the neck without disturbing the patient. The rubber balloons are attached to a tap by 2 separate tubes (Figs. 1 and 2). By turning the handle of the tap to the right or left, the desired carotid artery is attached to the oscillometer. This enables us to control and compare the 2 carotids without removing the collar. After measuring one side, the balloon is deflated. Then the other balloon is inflated. The pressure of the oscillometer can be raised gradually to 280 mm. Hg or higher without respiratory difficulty, because the pressure is one-sided and the fore-edge of the rubber does not obstruct the trachea. A comparison of the 2 carotid arteries and a recording of the findings can be easily accomplished within five minutes. The following should be considered carefully:

1] Whether the maximal oscillation (oscillometric index) is within the normal range can be decided.

2] Whether there is asymmetry between the two sides during the oscillation.

The procedure is carried out at normal room temperature with the patient in a sitting or standing position. Pressure should be increased gradually. If there is clinical evidence of carotid occlusion, the occlusive side should be examined first and the pressure decreased immediately after examination. If the occlusion is complete on one side, the examination of the other side should be done in the supine position and with great care. Results are recorded in the same manner as peripheral vessel recordings (Fig. 3). The cuff is used to determine carotid blood pressure either by the oscillometric or auscultative method.

From the Department of Neurology, Gülhane Army Medical Center (Postgraduate School), Ankara, Turkey.
Read at the monthly meeting of the Faculty of Medicine, Ankara, April 30, 1960.

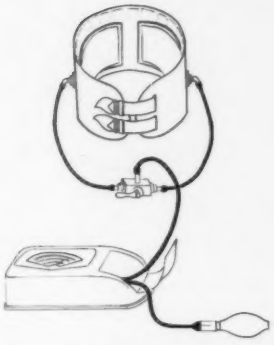


Fig. 1. The collar with the double balloon prepared for bilateral oscillometry and its connection to the oscillometer.

Fig. 2. The patient prepared for examination

Oscillometric method. Using a sensitive oscillometer, it is as easy to determine carotid blood pressure as to determine brachial blood pressure. Besides the systolic and diastolic pressures, there is a mid-pressure equal to half the total systolic and diastolic pressures; it decreases and increases with their respective decrease and increase. In a normal adult, this mid-pressure is 100 mm. Hg. The midpressure determined by the oscillometer constitutes the oscillometric index (the instant when excursion is greatest).

Systolic and diastolic pressures of the carotid artery are also determined by the oscillometer but are not so clear-cut nor so easy to determine as the mid-pressure. If the pressure of the oscillometer is gradually increased, the minimal excursions that begin with low pres-

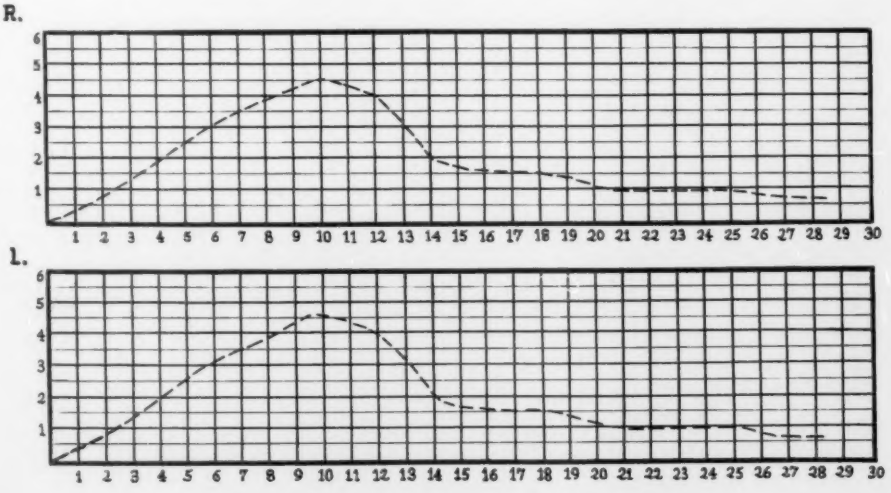


Fig. 3. Bilateral carotid oscillogram of a normal subject

Fig. 4. Oscillogram showing relationship between diastolic pressure, midpressure, and systolic blood pressure (after Chiray and Chéne)

sures will broaden. This first broadening of the pressure scale indicates the diastolic pressure. At the maximal excursion, the scale shows the mid-pressure. If one further increases the pressure, the oscillation decreases. This first decrease represents the systolic pressure[2] (Fig. 4).

Auscultative method. Using the collar previously described, carotid blood pressure can be determined in the same way as brachial blood pressure. Carotid sound may not disappear even under high pressures. This may result [1] from the softness of neck tissues preventing complete obstruction of the carotid artery and [2] from the collateral circulation that supplies the artery. When using this method, it is necessary to recognize the changing sounds of the carotid artery. For this reason, we prefer the oscillometric method as the easier and more reliable procedure to employ.

RESULTS

Subjects in this study were divided into 3 groups. The first group consisted of 50 normal subjects (30 men and 20 women). Blood pressures of this group were within normal limits. The maximal oscillation level (oscillometric index) of the carotid artery in these normal subjects was between 2 and 6. At the beginning, at the point of maximal deflection, and at the end of the oscillograms, carotid arteries on the two sides were symmetrical in these normal subjects.

The second group of subjects consisted of different types of nonvascular neurologic cases. The third group consisted of subjects in whom there was evidence of new and old hemiplegic aphasic disease of vascular origin and advanced cerebral arteriosclerosis. In some of these cases, evident asymmetry and oscillometric index differences were observed. The record obtained from a 65-year-old nonsyphilitic subject (C.A.), who had hemiplegia on the right and slight hemiparesia on the left, showed evident asymmetry that confirmed the clinical findings (Fig. 5). In this case, pressures of the central retinal arteries were also

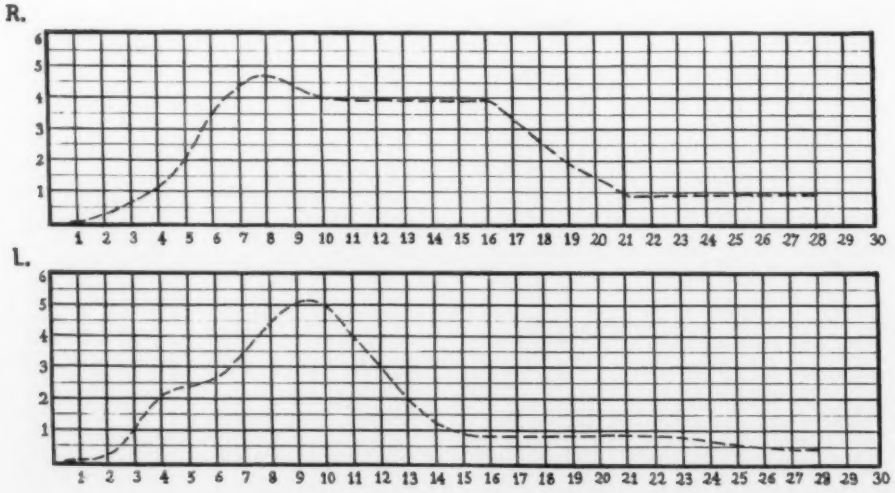


Fig. 5. Trace of a patient (C.A.) with a history of cerebral arteriosclerosis

different by ophthalmodynamometry. These findings are to be verified in indicated cases by angiography; they will be reported in detail later.

In the supine position, blood pressures of the brachial, femoral, and carotid arteries are equal in normal subjects. The effect of gravity makes the femoral pressure higher when the subject stands; and the difference is equal to the pressure of the blood column between the 2 positions. The autonomic nerve system (especially with splanchnic area arteries) controls and protects the cerebral circulation against gravity.

The midpressure of the 2 carotid arteries, when determined by oscillometer, can be seen on the tracings.

DISCUSSION

The diagnosis of narrowing and occlusion of the common carotid and internal carotid arteries is helpful in explaining the commonest symptoms such as hemiplegia, aphasia, convulsions, and unconsciousness. Such a diagnosis also helps in evaluating the prognosis and results of treatment.

Despite clinical findings of carotid narrowing and occlusion, it is always necessary to apply objective investigation methods for definite diagnosis. In 80% of carotid occlusion cases, there is early or late hemiplegia on the side opposite the occlusion; hemiplegia has been preceded by transient hemiparesis, monoparesis, or aphasia. Monocular blindness, unconsciousness, and focal or generalized epileptic seizures may also occur. Headache is a common symptom. The intermittent symptoms often reflect diminution in the systemic blood pressure from some cause. Transient or permanent monocular blindness on the side of occlusion is present in only 15 to 25% of cases.

Pulseless disease may be confused with carotid thrombosis. The chief symptoms of pulseless disease, described in 1908, are: [1] vertigo; [2] epileptiform convulsions and hemiplegias; [3] absence of pulsation in the common carotid on one or both sides; [4] transient blindness; [5] rapidly developing cataract and optic nerve atrophy; [6] decreased intraoptic arterial pressure; [7] intermittent claudication of the arms; and [8] absence of subclavian, brachial, and radial pulses, with decreased or imperceptible pressures in the upper extremities and increased pressure in the lower extremities. Those patients whose cases have been best documented have had syphilitic aortitis or aneurysms. The remainder have had other evidence of obliterative arteriosclerosis. The syndrome occasionally occurs in young or middle-aged women who show no other evidence of arteriosclerosis.

Carotid ligation may be useful for several different purposes. Before applying such ligation, a diagnosis of carotid occlusion from the clinical findings may be most helpful. Although angiography is the most reliable and definite diagnostic method, it is not suitable to apply in every case. In occlusion and severe narrowing, the results of ophthalmodynamometric studies are also questionable for diagnostic purposes. Besides, it is not possible by this method to differentiate between common carotid artery occlusions and internal carotid artery occlusions.[3] Palpation of the carotid artery is of value only in pulseless disease and in complete obliteration of the carotid artery. Partial occlusions of the carotid artery cannot be determined by this method of examination.

Carotid oscillometry is easy to manage and is harmless as blood pressure determination. We did not observe a single complication, not even an insignificant one, in applying this procedure to more than 100 cases. Carotid oscillometry may be useful for the following conditions:

1] In thrombotic involvement of the common carotid artery, from the beginning of narrowing till complete obliteration.

2] In vascular accidents such as hemiplegia, aphasia, unconsiousness and convulsions and in diseases such as arteriosclerosis, syphilis, diabetes mellitus, thromboangiitis obliterans, embolus, neoplastic pressure on arteries, vasospasm, and aneurysms. The diagnostic method helps to determine the degree of the process, the prognosis, and the rational basis of treatment.

3] By repeated measurements, in the diagnosis of intermittent insufficiency.[4]

Carotid artery pressure indicates the sufficiency of the collateral circulation; it should therefore be considered before applying carotid ligation for aneurysms. It is very im-

portant to know the effects of carotid ligation before its execution. Two methods are used for this purpose.

1] The carotid that is to be ligated can be manually compressed. Subjects who tolerate the one-hour compression are apt to have adequate collateral circulation. It is possible to apply one-sided pressure for the desired duration by using the collar previously described.

2] Some authors measure intracarotid pressure by means of a tube inserted in the carotid artery. The carotid artery is compressed without removing the tube; this naturally decreases the pressure. Normally this decrease is approximately 50% and is directly proportional to the collateral circulatory condition. More than a 60% decrease indicates weak collateral circulation and poor results after ligation.[5] This test may be made with the oscillometric method in the same way. By manually compressing the carotid artery at the lower edge of the collar, the decrease in pressure may be obtained.

Complementary investigations on wide statistical materials will show that measuring carotid pressure is important as a prodromal finding and as a control on treatment and prognosis in various vascular cerebral lesions.

CONCLUSIONS

The lesion of the occlusive disease of the internal carotid artery is mainly seen at the level of the carotid sinus; the process involves the common carotid artery to some degree in almost every case. Bilateral carotid oscillometry measurement is a direct and easy method for early diagnosis of the occlusive disease of the common carotid artery. This diagnostic measurement should be done systematically on all hemiplegic, aphasic, unconscious, or convulsive patients and on patients who show evidence of dementia. Repeated examinations disclose intermittent carotid insufficiency.

Essentials of this diagnostic method consist of [1] determining whether the oscillometric index is within normal limits and [2] obtaining bilateral measurement and comparison of the two carotid artery pressures. Before carotid ligation for treatment purposes is attempted, carotid artery pressure may be used as a test of whether collateral circulation is sufficient.

REFERENCES

1. Wood, A., and Toole, F.: Carotid artery occlusion and its diagnosis by ophthalmodynamometry. J.A.M.A. 165:1264, 1957.
2. Chiray, M., and Chene, P.: Semiologie Médical, traduction by N. Ö. Irdelp. Istanbul, Ahmed Ihsan matbaasi, 1935, pp. 108-109.
3. Heyman, A., Karp, H. R., and Bloor, B. M.: Determination of retinal artery pressures in diagnosis of carotid artery occlusion. Neurology 7:97, 1957.
4. Millikan, C. H., Siekert, R. G., and Whisnant, J. P.: Intermittent carotid and vertebral-basilar insufficiency associated with polycythemia. Neurology 10: 188, 1960.
5. Jacquemart, A.: Les anévrismes intracraniens. Hôrizons Médicaux 4:14, 1954.

Electrolyte distribution in mammalian central nervous system

Are glia high sodium cells?

Robert Katzman, M.D.

RECENT STUDIES of the mammalian central nervous system utilizing microelectrodes and electron microscopy necessitate a reworking of concepts concerning electrolyte distribution and fluid spaces within mammalian brain. It is the purpose of the present report to review pertinent information now available, explore certain consequences of the hypothesis identifying glial cell with the brain extracellular fluid space, and present preliminary data relevant to this hypothesis.

EVIDENCE FROM MICROELECTRODE STUDIES

Measurements from membrane and action potentials of central nervous system neurons have been made by intracellular recording utilizing fine microelectrodes inserted into cat motor neurons, Betz cells, and a variety of other cells.[1] It has been found that, upon entering a neuronal cell body with a microelectrode, a large negative potential is encountered. This potential remains fairly stable after the cell has recovered from the initial injury and is presumed to represent the membrane potential. Upon this membrane potential are superimposed positive action potentials usually 5 to 20 mv. greater than membrane potential. In the case of the spinal motor neuron and the Betz cell, these spikes can be set up by antidromic stimulation of the axon in the ventral root and medullary pyramid and positive identification of the cells thereby achieved.[1,2]

The electrical sign and amplitude of the membrane and action potentials recorded in the mammalian central nervous system are similar to those recorded in the single nerve and muscle fibers that have been studied with intracellular microelectrodes. A few examples are given in Table 1. A certain arbitrariness about these values exists, since some workers reject cells with low membrane potentials, assuming, with justification, that such cells have been injured during the insertion of the microelectrode.[1] Even when this selectivity is consciously avoided and results showing a very wide scatter of potentials are published, the membrane potential of mammalian central nervous system neurons averages out to about −50 mv. and the action potential is about 60 mv.[5]

In the single nerve and muscle fiber, the intracellular concentration of sodium and potassium are exactly known since the fibers have been analyzed chemically. In the case of the squid giant axon, the axoplasm has been extruded and analyzed directly for sodium and potassium.[6,7] The extracellular concentration of sodium and potassium is determined by whatever medium is used for soaking the fibers. By manipulating the ionic composition of the external medium, it can be shown that, to a first approximation, the membrane potential is established by an electrochemical potential set up by the concentration gradient of potassium, which is present in high concentration inside the cell and in low concentration outside; the action potential is established by the concentration gradient of sodium, high outside the cell and low inside. During the

From the Division of Neurology, Department of Medicine, Albert Einstein College of Medicine, and The Bronx Municipal Hospital, The Bronx, New York.

This work was supported by fellowships from the National Multiple Sclerosis Society 1958-1959 and the Parkinson Foundation 1959-1960 and by Grants B 1450 C1 and 2M-6418 C2 from the U. S. Public Health Service.

Presented as the S. Weir Mitchell Award Essay at the twelfth annual meeting of the American Academy of Neurology, Miami Beach, April 29, 1960.

TABLE 1
EXAMPLES OF INTRACELLULAR POTENTIALS MEASURED WITH MICROELECTRODES
(VALUES GIVEN ARE MEANS)

Cell	*Resting potential*	*Action potential*	*Overshoot of action potential*	*Reference*
Giant axon, Loligo	–48 mv.	88 mv.	+40	3
Giant axon, Sepia	–62 mv.	120 mv.	+58	3
Striated muscle fiber, frog	–88 mv.	119 mv.	+31	3
Heart Purkinje cell, dog	–90 mv.	121 mv.	+31	3
Betz cell, rat	–61 mv.	65 mv.	+ 4	2
Spinal motor neuron, cat	–70 mv.	90 mv.	+20	4

resting state, the nerve fiber is more permeable to potassium; during the passage of the nerve impulse, there is a transient but very large increase in sodium permeability and a concomitant decrease in potassium permeability, so that the sodium concentration gradient determines the recorded potential. The movements of sodium and potassium ions predicted by this theory have been directly measured using radioactive tracers, confirming the hypothesis.[3,6] Such work has also produced evidence that the inequality of electrolyte concentrations is maintained by a sodium extrusion pump acting in the cell membrane.

While the amplitude of the membrane potential and the action potential in large fibers responds to changes in the external media as if the potentials were generated by the concentration gradient of ions across the membrane, microinjection of ions into the axoplasm does not produce the predicted changes.[7] Consequently, Grundfest[7] has postulated that these potentials are due to diffusion potentials set up by a sodium extrusion mechanism in the membrane rather than to the concentration gradient of ions secondarily created by this pumping mechanism. However, here again, such a mechanism would result in the cells containing high potassium concentrations and the external environments high sodium concentrations.

In the mammalian central nervous system, the intraneuronal and extraneuronal concentrations of sodium and potassium have not been measured directly. Nevertheless, Eccles[1] has assumed that the ionic hypothesis and Grundfest,[7] the ionic pump hypothesis can be applied directly to this system.

The most important evidence favoring the application of these hypotheses to the mammalian central nervous system is that the sign and amplitude of the membrane and action potentials recorded in mammalian brain are similar to those observed in the invertebrate giant axons and the vertebrate muscle fibers studied. In addition, injection of ions into the cat motor neuron through a double barreled microelectrode produces changes similar to those seen with microinjection into the squid giant axon.[4,7] Nevertheless, the lack of direct chemical analyses of central nervous system neurons constitutes a significant gap in our knowledge that precludes the definite application of these hypotheses at present.

EVIDENCE FROM DIRECT CHEMICAL ANALYSIS OF BRAIN TISSUE

Reported water and electrolyte concentrations in the brain of the dog, rabbit, rat, and mouse are summarized in Table 2. Values for muscle and plasma concentrations in the dog and rat are given for comparison. The values are expressed in milliequivalents per kilogram of fresh material. It can be seen that the concentration of potassium is similar in all the species and is the same in brain and in muscle. The sodium and chloride concentrations are higher in the brain than in muscle, more so in the dog and rabbit than in the rat or mouse.

The electrolyte concentrations in Table 2 are expressed in milliequivalents of ion per kilogram of net weight. In Table 3, the data have

TABLE 2
ELECTROLYTE CONCENTRATIONS IN NORMAL ANIMALS
PER KILOGRAM OF FRESH WEIGHT

	Number of animals	H_2O (gm. per kg.)	mEq. per kg. Na	K	Ca	Mg	Cl	Reference
Brain								
1. Dog	14	763	51.8	95.4	2.1	11.2	36.3	8,9
2. Rat	12	813	47.2	99.8			28.0	10,11
3. Rat	30		48.0	100.9				12,13
4. Rabbit	2	812	52.1			11.8	32.7	15
5. Mouse	6	797	42.4	105.5			28.7	14
Muscle								
6. Dog	14	767	29.2	98.1	1.9	16.3	19.4	8,9
7. Rat	6	734	20.7	99.4			13.9	10,11
Plasma								
8. Dog	2	930	150.5	5.3	4.9	1.8	108.0	8,9
9. Rat	12	919	142.1	6.0	5.5		104.6	10,11
10. Rat	30		137.5	5.5				11,12

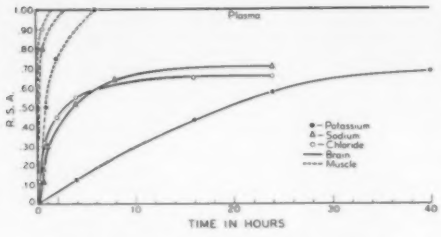
been recalculated as millimols per kilogram of water, hence as milliosmols. The total milliosmols of cation in dog brain is 202 as compared to 178 in dog muscle and 171 in dog plasma. There are therefore 24 milliosmols more of cation in the dog brain than in muscle tissue. In the rat brain, there are 14 milliosmols more of cation than in rat muscle. Again, the osmols of electrolytes in dog brain exceed that in dog muscle by 46, and in rat brain the excess is 29. It is apparent that the surplus electrolyte consists of sodium and chloride, both greater in brain than in muscle.

Maffly and Leaf[16] have measured the melting point of frozen rat brain and have shown it to be isosmotic with plasma, liver, kidney cortex, and muscle from the same animal. Hence, it must follow that either the anions in brain contain many large molecules with multiple anionic sites so as to provide electrical neutrality but contribute little to the osmolality of the tissue or, alternately, some of the cation must be bound in an unionized form. Christensen and Hastings[17] found that an aqueous suspension of cephalin, a mixture of lipids that includes the acidic lipids, phosphatidyl serine, and diphosphoinositide does bind sodium and potassium. Folch[18,19] and Manery[20] have suggested that this may occur in vivo, accounting for the apparent surplus of cation in brain tissue.

The concentrations of cations in the brain

TABLE 3
ELECTROLYTE CONCENTRATIONS AS MILLIOSMOLS
(MILLIMOLES PER KILO OF H_2O)

	Recalculated from line	Number	Na	K	Ca	Mg	Total cation	Cl	Total electrolyte
Brain									
Dog	1	14	68	125.0	1.4	7.3	201.7	47.6	249.3
Rat	2	12	58	122	(1)	(7)	188	34.5	222.5
Muscle									
Dog	6	14	38	128	1.2	10.6	177.8	25.3	203.1
Rat	7	6	28	135	(1)	(10)	174	19.0	193
Plasma									
Dog	8	2	162	5.7	2.6	1.0	171.3	116	287.3
Rat	9	12	155	6.5	3.0	(1)	165.5	114	279.5



Uptake of radioactive isotopes of potassium, sodium, and chloride by brain and muscle tissue after intraperitoneal or intravenous injection. The data, averaged from that available in the literature,[21-27] has been recalculated as R.S.A. or relative specific activity, that is, counts / minute in tissue / mEq. in tissue / counts / minute in plasma / mEq. in plasma.

is largely independent of cations in the blood. Thus, Leiderman and Katzman[21] and Davenport[10] found the brain potassium to be unchanged in chronic adrenalectomized rats at the time plasma potassium has risen about 50%. Conversely, the injection of DOCA or aldosterone lowers plasma potassium but does not alter the concentration in the brain.[11,14,22] This remarkable constancy of the brain cation pool may be due, in part to the special transport mechanisms present for moving ions from plasma into the brain. In the figure, the appearance in the brain of parenterally injected radioactive isotopes of Na, K, and Cl are shown and compared with the appearance rate of these same isotopes in muscle. The slowness with which these isotopes enter the brain is an example of the function of the blood-brain barrier. In contrast, radioactive ions injected into the subarachnoid space enter the brain quite rapidly.[21,25]

EVIDENCE FROM ELECTRON MICROSCOPY

Electron micrographs of the brain show neurons, glia, and their processes packed closely together with only gaps of 100 to 200 Å. between their membranes.[28-30] There is no extracellular space such as can be seen in other tissues. This finding has been repeatedly observed and appears to be solidly established.

Moreover, recent work with the electron microscope indicates that, in those states in which brain tissues swells, the swelling takes place within the cytoplasm of glial cells, probably astrocytes. This has now been reported for swelling in vitro of brain slices and in vivo around stab wounds, areas frozen with dry ice, and brain tumors and in the generalized edema of triethyl tin intoxication.[30-32]

Earlier workers had assumed the existence of an extracellular space in the brain similar to the one that exists in muscle tissue. Woodbury[14] had equated this to the chloride space of the brain, that is, the volume of brain water that would be occupied by the chloride of the brain if it were in equilibrium with serum chloride. The assumption of the existence of this chloride had proven useful in explaining the effect of various agents on seizure threshold. Allen[33] determined an inulin and ferricyanide space of 14 to 17% in brain slices, taking into account the changes that occur during incubation of slices in vitro. With the evidence from electron microscopy, the chloride, inulin, and ferricyanide spaces can no longer be equated with an extracellular space, yet they still may be physiologically valid concepts.

A third important observation of electron microscopists pertinent to the present problem is the intimate relationship of axons to glial cells, presumably oligodendroglia. Luse[34] had presented evidence that central nervous system myelin was laid down by glial cells. De Robertis[35] has found that glial cells are actually impaled by axons—that the axons are embedded within the cytoplasm of the glial cell. Myelin is laid down with the glial cell by the wrapping of endoplasmic reticulum around the axon. Hence, myelin is an intraglial inclusion, and the medium surrounding the axon is the glial cytoplasm.

HYPOTHESES

Of the possible ways of distributing the electrolytes of the brain so as to satisfy both the physiologic and anatomic evidence, two will be presented. In order to simplify discussion, only the major cations, sodium and potassium, are considered.

1. The extracellular fluid of the brain, consisting of an ultrafiltrate of plasma, is confined to the small 100- to 200-Å. spaces that exist between cell membranes. Horstmann and

Meves[36] have calculated that, in areas in which the cellular elements are only 0.1 μ in diameter, the volume represented by 200 Å. with cellular gaps would represent 30% of the total volume of the region, assuming the cellular elements to be cylinders. In regions in which the average diameter of cellular elements is 0.5 μ, this extracellular volume falls to 5%, and, if the cellular elements average 1 μ in diameter, the value is 3.5%. Actual measurements of electron micrographs of the optic tectum of the shark gave values ranging from 2.5 to 10.6%, with a mean value of 4.6%. Comparable measurements are not available for mammalian brain, but, since the cellular processes are somewhat larger than in the shark and the extracellular space somewhat smaller, a value between 3 and 5% would be reasonable.

Assume that the extracellular space represents 4% of the fluid space of the brain and that in the remaining 96% the remaining sodium and potassium are uniformly distributed. In a brain containing sodium in the concentration of 60 mEq. per kilo of H_2O and potassium in the concentration of 120 mEq. per kilo of H_2O, the distribution in a kilo of brain H_2O would be as follows:

	Extracellular (mEq.)	Intracellular (mEq.)
Na	160	$\frac{60 - 160\ (.04) = 56}{0.96}$
K	6	$\frac{120 - 6\ (.04) = 125}{0.96}$

Using these figures, the maximum membrane and action potential that could be generated by the concentration gradients of the ions can be calculated. For the membrane potential, dependent upon potassium ion, the value would be

$$-58 \log_{10} \frac{\text{K intra}}{\text{K extra}} = -58 \log_{10} \frac{125}{6} = -75 \text{ mv.}$$

For the action potential, dependent upon the sodium ion, the value would be

$$-58 \log_{10} \text{Na} \frac{\text{intra}}{\text{extra}} = -58 \log_{10} \frac{56}{160} = +27 \text{ mv.}$$

These values are in good agreement with the value for the membrane potential and the sodium overshoot listed in Table 1.

An additional assumption that must be made is that the membranes of the extraneuronal cells are at low resistance, permitting the flow of currents associated with action potentials through them. This is necessary as the resistance to current flow offered by the small extracellular cannaliculi would be much too great. Membranes elsewhere are known that maintain ionic gradients and possess resting potentials, yet act as low resistance pathways for the flow of currents; an example is the membrane on one side of the electroplaque that does not generate an action potential but permits the currents of action potential from the opposite membrane to flow through it.

In favor of this hypothesis is the finding that astroglia in tissue culture exhibit a membrane potential up to −50mv. when studied with electrodes.[37] Since this potential is generated by the cells surrounded by a low potassium and high sodium medium, it may be speculated that they are high potassium cells. Direct chemical analyses have not been reported.

During exploration of the mammalian cortex with microelectrodes, many cells are encountered with membrane potentials that do not generate action potentials. While these may represent neurons, other workers believe that they may be astrocytes.

Against this hypothesis is the finding by De Robertis[35] of axons completely surrounded by glial cell cytoplasm, so that no cannaliculi containing extracellular fluid could reach such axons. However, saltatory conduction may occur in these axons, and such cannaliculi may be present in the nodal areas.

2. There are two compartments in mammalian brain, a neuronal compartment with high potassium and low sodium and an extraneuronal compartment consisting of glial cells with a low potassium and high sodium content.

That glial cells may have a role in neuronal nutrition was suggested by del Rio Hortega,[38] who was impressed with the location of oligodendroglia as neuronal and axonal satellites and by the relationship of astroglia to the capillary wall. This view has recently been reemphasized.[30] The transport of ions and water from the capillary to the neuron has been ascribed to astroglia; the consequent slowness of ionic movement through the astroglia would account for the blood-brain barrier phenom-

enon. Still another function ascribed to astroglia would be to act as an environment for the maintenance and replacement of gradients of K and Na at the bioelectrically active surface membrane of the neurons.[26]

The demonstration that some axons are surrounded by the cytoplasm of oligodendroglia would suggest that these cells rather than astroglia are involved in this function. Moreover, if only the oligodendroglia were high sodium cells and the astroglia were high potassium cells, the membrane potentials of the astroglia would be accounted for. This hypothesis would be consistent with both the physiologic and anatomic evidence we have reviewed.

If, indeed, astroglia, oligodendroglia, or both provide an extraneuronal environment suitable for the generation of potentials at the neuronal surface membrane in a manner akin to that seen in other excitable cells, it should follow that such cells contain a high sodium and low potassium concentration. This consequence, that those glial cells acting as an extraneuronal equivalent of an extracellular environment have a high sodium and low potassium concentration, is important since it is potentially testable. The direct approach would be to separate glial cells from neurons and determine their sodium and potassium concentrations. Glial cells can be concentrated using centrifugation in sucrose solutions.[39] Such a method is not applicable to the present problem, since artifactual exchange of sodium and potassium ions occurs when tissue or chemicals are processed in vitro in aqueous or alcoholic solutions in which the cations are highly soluble.[13,19] The use of nonpolar solvents might eliminate this problem. However, such a separation has not been accomplished yet.

In the absence of methodology allowing for the direct determination of sodium and potassium concentrations inside glial cells, indirect evidence must be sought, two types of which will now be reported.

EXPERIMENTAL EVIDENCE

Relative sodium-potassium concentrations present in chloroform extracts of frozen brain tissue

Methods. The methods used will be reported in detail elsewhere[40] but may be briefly summarized. Slices of rat or cat brain tissue, 1 to 2 mm. in thickness, are obtained at operation or immediately after decapitation, weighed on a torsion balance, and frozen at −140° C. in isopentane cooled with liquid nitrogen. The slice is then extracted for two to four days at −45° C. in 150 volumes of chloroform. The solvent is then removed through a cinter glass filter stick, dried under an infrared lamp with a stream of nitrogen, weighed, and analyzed. Utilizing this method, 35 to 55% of white matter lipid and 40 to 60% of gray matter lipid are extracted. The extract is free of chloride, 97% nondialyzable, and easily redissolved in chloroform, thus appearing to be almost pure lipid. A typical extract of white matter (compared to a Folch extract of the same tissue) is as follows:

	Analysis of extracted material		
	% P	*% cholesterol*	*% cerebroside*
Folch	1.7	21	26
$CHCl_3$(−45°)	1.2	53	8

	% of tissue lipid extracted			
	Lipid	*P-lipid*	*Cholesterol*	*Cerebroside*
Folch	100	100	100	100
$CHCl_3$(−45°)	38	27	96	11

The extracted material contains small amounts of cation, about 0.15 to 0.35 mEq. of sodium plus potassium per milligram of extract. Since the chloride present is less than one-tenth of this, this cation is presumed to be present as the cation of acidic lipids. Phosphatidyl serine has been identified in the extracts but not yet quantitatively determined. Because of the very low amounts of cation present, special cautions must be taken to guard against contamination by extraneous sources of sodium and potassium. All glassware utilized is specially soaked in nitric acid and rinsed with deionized water; 1 blank tube containing chloroform is set up for each 2 tubes of chloroform plus tissue. Despite these precautions, contamination occurs intermittently as found by analysis of the blank tube. When found, the entire run was discarded.

Analyses of sodium and potassium are carried out as described below; chloride was analyzed by the method of Lowry.[41]

Results. The usual method of extracting

lipids, such as homogenization of brain tissue with Folch solution (2:1, chloroform : methanol) or extraction with ether after washing with acetone, results in rapid equilibration of cations such that the final lipid cation contains about 1 mEq. of Na for each 2 mEq. of K, the same ratio as in the original brain tissue.[17,19] This equilibration occurs through the use of water or relatively polar organic solvents, such as the alcohols or acetone, which are miscible with the tissue water and in which the inorganic salts of the cation are soluble. By the use of chloroform, in which the solubility of most salts of the cations is sharply limited, and by carrying out the procedure at −45° C., at which temperature the aqueous soluble salts of sodium and potassium are kept immobile in the aqueous phase of the tissue, equilibration of cations is reduced during extraction and the final lipid cation is largely that found with the lipid in vivo rather than an artifact of the extraction procedure.

The efficacy of this procedure in reducing interchange of cations can be detremined by the use of the radioisotopes Na^{24} and K.[42] If Na^{24} Cl (or K^{42} Cl) is mixed with Na cephalin (or K cephalin) in a Folch solution, equilibration will occur in minutes such that the lipid cation will contain a mixture of Na^{24} and Na in whatever ratio these isotopes are present in the entire solution. If Na^{24} Cl is mixed with an equimolar amount of Na cephalin in chloroform at −45° C., this equilibration does not occur. After twenty-four hours, the specific activity of the lipid is only 0.6% of that of the added radioactive salt. If the mixture is vigorously homogenized, more interchange of cations occurs, but, after two hours of such homogenization, the specific activity of the lipid is still only 1.2% of that of the radioactive salt.

The ratio of mEq. of Na : mEq. of K obtained in such extracts is shown in Table 4.

Comment. The method of extraction of acidic lipid cation from frozen tissue was developed to study the kinetics of the exchange of acidic lipid cation in vivo, but the results listed in Table 4 are pertinent for our present problem. Since acidic lipid cation readily equilibrates with the cation of the surrounding media in aqueous suspensions, it must be assumed that in vivo the lipid cation equilibrates with the cations in the adjacent tissue water. Hence, when the ratio of mEq. of Na : mEq. of K in such extracted cation is greater than 0.6, approaches in fact 2.0, it may be assumed that part of the extracted lipid was obtained from a cell or intracellular region with a high sodium content. Whether this high sodium region is to be found in glial cells is not known since the source of the extracted acidic lipid has not been determined. However, it can be inferred that the distribution of the tissue cation is heterogeneous — that there are cells or cell compartments in the tissue in which sodium is the predominant cation. It then follows that the first hypothesis discussed above, that the sodium and potassium are distributed homogenously throughout the cellular elements of the tissue, can be discarded.

Relative sodium and potassium concentrations in glial cell tumors

Methods. Specimens of intracranial tumors 100 to 500 mg. in weight were obtained at operation. Care was taken by the surgeons to avoid moistening the specimen with saline. The tissue for electrolyte analysis was placed in a dry test tube. An adjoining piece of tissue was submitted for routine pathologic investigation.

The tumor tissue to be analyzed was divided into 3 parts: 1 for determination of the ratio of wet to dry weight, 1 for determination of blood content by a quantitative benzidine method,[12] and 1 for sodium and potassium determination by internal standard flame photometry after nitric acid digestion of the tissue.[12]

The specimens were received in the laboratory at different times after removal and had undergone variable degrees of drying. Consequently, the wet weight determinations were found to be of little value and the results have been expressed in relative concentration—that is, milliequivalents of sodium per milliequivalents of potassium—this ratio being invariant during drying.

Results. The relative Na : K concentrations in 8 gliomas are shown in Table 5, along with a few comparative sodium-potassium ratios.

Comment. The average mEq. of Na : mEq. of K of glial tumors in Table 5 is 1.8. Does this indicate that glial cells from which tumors

TABLE 4
RELATIVE SODIUM AND POTASSIUM CONCENTRATIONS IN LIPID EXTRACTED FROM FROZEN BRAIN TISSUE WITH CHLOROFORM AT −45° C.

	Weight of extract (mg.)	*μEq. K*	*μEq. Na*	*μEq. Cl*	*μEq. of Na: μEq. of K*
Cat					
Cortex	5.2	.14	.41	<.05	2.9
White matter	10.9	.30	.44	<.05	1.3
Rat					
Cortex	4.0	.48	.24	<.05	2.0
Brain stem	11.0	.58	.77	.10	1.3

are derived contain about 2 mEq. of Na for each 1 mEq. of K? To what extent does the electrolyte distribution of tumors reflect that of the parent tissue and to what extent does it depend upon other factors such as the degree of cellularity, the amount of stroma produced, and the amount of necrosis in the tumors?

These questions cannot be resolved. The present series is small. Reliable data in the literature is sparse. In squamous cell carcinoma[42] produced in mouse skin by implantation of methyl cholanthrene, the relative mEq. of Na : mEq. of K had changed only 5% from that found in normal epidermis. After 30 transplantations, some difference was seen between the electrolyte distribution of solid tumors in which the mEq. of Na : mEq of K was 0.7 and necrotic tumors in which the ratio was 1.1. Among testicular carcinomas,[43] the mEq. of Na : mEq. of K of tumors with low fat was found to be 0.34 and with high fat 0.58, as compared to a ratio of 0.55 in the parent tissue. An increase in the potassium content of tumors relative to parent tissue has been reported for gastric carcinoma[44] and has been ascribed to the greater cellularity of these tumors. It is also found in intestinal carcinoma[45] and other tumors.[46] Contrary to these results is a report[47] indicating that the

TABLE 5
RELATIVE SODIUM AND POTASSIUM CONCENTRATIONS IN INTRACRANIAL TUMORS

	Location	*Estimated cellularity*	*mEq. of Na: mEq. of K total sample*	*% of blood*	*mEq. of Na: mEq. of K corrected for blood*
1. Astrocytoma	Third ventricle	+	2.9	(9)*	2.9
2. Astrocytoma	Cerebellum	+++	2.9	8	2.9
3. Glioblastoma	Hemisphere	+++	2.7	3	2.7
4. Glioblastoma	Hemisphere	+++	2.3	5	2.2
5. Glioblastoma	Hemisphere	++++	1.7	(9)*	1.5
6. Astrocytoma	Hemisphere	++	1.5	(9)*	1.3
7. Astrocytoma (cystic)	Hemisphere	++	1.3	3	1.2
8. Glioblastoma	Hemisphere	++	1.2	5	1.1
9. Mixed oligo- and astrocytoma	Hemisphere	+++	1.2	8	1.0
10. Astrocytoma	Hemisphere	++	1.3	20	.9
11. Cortex (case 6)			.65	6	.61
12. Blood (hematocrit 35)					3.0
13. Metastatic carcinoma	Hemisphere	++	.83	3	.8
14. Metastatic carcinoma	Hemisphere	+++	.8	9	.6
15. Metastatic carcinoma	Hemisphere	+++	.7	4	.6

*Assumed

mEq. of Na : mEq. of K fluctuates widely among malignant tumors, ranging from 0.3 to 9. The analytic procedure reported by these authors[47] contains a step in which the tumor tissue is defatted with mixtures of ethanol-ether and ethanol-chloroform instead of the usual diethyl ether–petroleum ether mixture. Both ethanol and methanol will remove large amounts of tissue electrolytes, salts of sodium and potassium being readily soluble in alcohols. Yet, it would be anticipated that such alcohol extractions would remove the sodium and potassium in relatively constant proportions. Hence, these results are disturbing.

Because of these uncertainties, no deduction concerning the mEq. of Na : mEq. of K in normal glial cells can be made with assurance. The present evidence, however, is consistent with the view that glial cells may be high sodium cells. It had been anticipated that oligiodendrogliomas might be even higher in sodium content than other glial tumors, but the single such tumor analyzed behaved as did other glial tumors. Hence, the present evidence is consistent with the view that glial cells may be high sodium cells and that various types of glial cells may act similarly in this regard. The evidence is suggestive enough to warrant an intensive search for methodology that will permit direct sodium and potassium analyses of normal glial cells.

CONCLUSIONS

Evidence concerning the distribution of electrolytes in mammalian central nervous system is reviewed. Studies of the electrical properties of central nervous neurons suggest that these neurons contain high concentrations of potassium and are bathed in a medium containing preponderantly sodium. Chemical analyses show that the whole tissue contains large amounts of sodium as well as potassium, on the average 58 mEq. of sodium per kilogram of fresh weight and 100 mEq. of potassium per kilogram of fresh weight. Evidence from electron microscopy indicates that the bulk of these electrolytes must be distributed between neurons and glial cells, the brain being filled with cellular elements with only 100- 200-Å. spaces between. Moreover, axons may be embedded in the cytoplasm of glial cells.

This evidence leads to alternative hypotheses: first, that sodium and potassium are homogeneously distributed throughout the cells, the small spaces between the cells functioning as an extracellular space to preserve the electrochemical gradient at membranes, and, second, that glial cells or a fraction of the glial cells act as the functional extraneuronal space to preserve the electrochemical gradients. The consequence of the second hypothesis is that the glial cells acting in this capacity should be high sodium cells.

Experimental data of 2 types are presented. The first demonstrates that extracts of brain acidic lipid contain cation with sodium predominating over potassium. This indicates that the sodium and potassium of the brain are not homogeneously distributed but that there must be formed elements with high sodium concentrations. Secondly, the mEq. of Na : mEq. of K of 10 glial cell tumors is found to exceed 1.0 with an average value of 1.8. While this finding must be applied with caution, it is consistent with the hypothesis that some or all of the glial cells may be high sodium cells.

The author wishes to thank Drs. Robert A. Fishman and Lawrence Pool and the staffs of the Neurosurgical Services of the Presbyterian Hospital and The Bronx Municipal Hospital for their assistance in obtaining tumor specimens and Mr. Clarence Wilson for his technical assistance.

REFERENCES

1. Eccles, J. C.: The Physiology of Nerve Cells. Baltimore, Johns Hopkins Press, 1957.
2. Phillips, C. G.: Intracellular records from Betz cells in the cat. Quart. J. Exper. Physiol. 41:58, 1956.
3. Hodgkin, A. L.: The ionic basis of electrical activity in nerve and muscle. Biol. Rev. 26:339, 1951.
4. Coombs, J. S., Eccles, J. C., and Fatt, P.: The electrical properties of the motoneurone membrane. J. Physiol. 130:291, 1955.
5. Frank, K., and Fuortes, M. G. F.: Potentials recorded from the spinal cord with microelectrodes. J. Physiol. 130:625, 1955.
6. Hodgkin, A. L.: Ionic movements and electrical activity in giant nerve fibers. Proc. Roy. Soc. B 148:1, 1958.
7. Grundfest, H.: The nature of the electrochemical potentials of bioelectric tissues. In Electrochemistry in Biology and Medicine, T. Shedlovsky, ed. New York, John Wiley, 1955, pp. 141-166.
8. Eichelberger, L., and Richter, R. B.: Water, nitrogen, and electrolyte concentration in brain. J. Biol. Chem. 154:21, 1944.
9. Manery, J. F.: Water and electrolyte metabolism. Physiol. Rev. 34:334, 1954.

10. Davenport, V. D.: Relation between brain and plasma electrolytes and electroshock seizure thresholds in adrenalectomized rats. Am. J. Physiol. 156:322, 1949.
11. Woodbury, D. M.: Effects of chronic administration of anticonvulsant drugs, alone and in combination with desoxycorticosterone, on electroshock seizure threshold and tissue electrolytes. J. Pharmacol & Exper. Therap. 105:46, 1952.
12. Katzman, R., and Leiderman, P. H.: Brain potassium exchange in normal adult and immature rats. Am. J. Physiol. 175:263, 1953.
13. Katzman, R.: Unpublished data.
14. Timiras, P. S., Woodbury, D. M., and Goodman, L. S.: Effect of adrenalectomy, hydrocortisone acetate and desoxycorticosterone acetate on brain excitability and electrolyte distribution in mice. J. Pharmacol. & Exper. Therap. 112:80, 1954.
15. Manery, J. F., and Hastings, A. B.: The distribution of electrolytes in mammalian tissues. J. Biol. Chem. 127:657, 1939.
16. Maffly, R. H., and Leaf, A.: The potential of water in mammalian tissues. J. Gen. Physiol. 42: 1257, 1959.
17. Christensen, H. N., and Hastings, A. B.: Phosphatides and inorganic salts. J. Biol. Chem. 136:387, 1940.
18. Folch, J.: In Biology of Mental Health and Disease, Milbank Memorial Fund Conference. New York. Hoeber, 1952, p. 133.
19. Folch, J., Lees, M., and Sloane-Stanley, G. H.: The role of acidic lipid in electrolyte balance of the nervous system of mammals. In Metabolism of the Nervous System, D. Richter, ed. New York, Pergamon Press, 1958, pp. 174-181.
20. Manery, J. F.: In Biology of Mental Health and Disease, Milbank Memorial Fund Conference. New York, Hoeber, 1952, pp. 124-132.
21. Leiderman, P. H., and Katzman, R.: Effect of adrenalectomy, desoxycorticosterone and cortisone on brain potassium exchange. Am. J. Physiol. 175:271, 1953.
22. Woodbury, D.: In Pincus, G., ed.: Recent Progress in Hormone Research. New York, Academic Press, 1954, Vol. 10.
23. Noonan, T. R., Fenn, W. O., and Haege, L.: The distribution of injected radioactive potassium in rats. Am. J. Physiol. 132:474, 1941.
24. Woodbury, P. M.: In Biology of Neuroglia, W. F. Windle, ed. Springfield, Ill., Charles C Thomas, 1958, pp. 120-125.
25. Rudolph, G. G., and Olsen, N. S.: Transfer of potassium between blood, cerebrospinal fluid and brain tissues. Am. J. Physiol. 186,157, 1956.
26. Manery, J. F., and Haege, L. F.: The extent to which radioactive chloride penetrates tissues. Am. J. Physiol. 134:83, 1941.
27. Manery, J. F., and Bale, W. F.: The penetration of radioactive sodium and phosphorus. Am. J. Physiol. 132:215, 1943.
28. Dempsey, E. W., and Luse, S.: Fine structure of the neurophil in relation to neuroglia cells. In Biology of Neuroglia, W. F. Windle, ed. Springfield, Ill., Charles C Thomas, 1958, pp. 99-119.
29. Wyckoff, R. W. G., and Young, J. Z.: The motor-neuron surface. Proc. Roy. Soc. B 144:440, 1956.
30. Gerschenfeld, H. M., Wald, F., Zadunaisky, J. A., and De Robertis, E. D.: Function of astroglia in the water-ion metabolism of the central nervous system. Neurology 9:412, 1959.
31. Torack, R. M., Terry, R. D., and Zimmerman, H. M.: The fine structure of cerebral fluid accumulation I. Swelling secondary to cold injury. Am. J. Path. 35: 1135, 1959.
32. Torack, R. M., Terry, R. D., and Zimmerman, H. M.: The fine structure of cerebral fluid accumulation. II. Swelling produced by triethyl tin poisoning and its comparison with that in the human brain. Am. J. Path. 36:273, 1960.
33. Allen, J. N.: Extracellular space in the central nervous system. Arch. Neurol. & Psychiat. 73:241, 1955.
34. Luse, S. A.: Formation of myelin in the central nervous system of mice and rats as studied with the electron microscope. J. Biophys. & Biochem. Cytol. 2:777, 1956.
35. De Robertis, E., Gerschenfeld, H. M., and Wald, F.: Cellular mechanism of myelinization in the central nervous system. J. Biophys. & Biochem. Cytol. 4:651, 1958.
36. Horstmann, E., and Meves, H.: Die Feinstruktur des molekularen Rindengraues und ihre physiologische Bedeutung. Ztschr. Zellforsch. 49:569, 1959.
37. Held, W., Chang, J. J., and Tasaki, I.: Electrical responses of astrocytic glia from the mammalian central nervous system cultivated in vitro. Experientia 14:220, 1958.
38. del Rio Hortega, P.: Quoted by A. A. Weil, in Textbook of Neuropathology. Philadelphia, Lea & Febiger, 1933, p. 335.
39. Korey, S. R., Orchen, M., and Brotz, M.: Studies of white matter. 1. Chemical constitution and respiration of neuroglial and myelin enriched fractions of white matter. J. Neuropath. & Exper. Neurol. 17:430, 1958.
40. Katzman, R., and Wilson, C.: Extraction of lipid and lipid cation from frozen brain tissue. J. Neurochem. In press.
41. Lowry, O. H., Roberts, N. R., Lerner, K. Y., and Farr, A.: The quantitative histochemistry of brain. 1. Chemical methods. J. Biol. Chem. 207:1, 1954.
42. Carruthers, C., and Suntzeff, V.: Chemical studies on the transformation of mouse epidermis by methylcholantherene to squamous cell carcinoma. J. Biol. Chem. 155: 459, 1944.
43. Huggins, C., and Eichelberger, L.: Studies on tumors of the testis. 1. Water and electrolyte content of testicular tumors and of normal, cryptorchid, and estrogenized testis. Cancer Research 4:447, 1944.
44. Brunschwig, A., Dunham, L., and Nichols, S.: Potassium and calcium content of gastric carcinoma. Cancer Research 6:230, 1946.
45. Dunham, L., Nichols, S., and Brunschwig, A.: Potassium and calcium content of carcinomas and papillomas of the colon. Cancer Research 6:233, 1946.
46. Shear, M. J.: The role of sodium potassium, calcium and magnesium in cancer: a review. Am. J. Cancer 18:924, 1933.
47. Waterhouse, C., Terepka, A. R., and Sherman, C.: The gross electrolyte composition of certain human malignant tissues. Cancer Res. 15:544, 1955.

The brain ACh-AChE-ChA system in respiratory control

Bernard Metz, Ph.D.

AN UNRESOLVED QUESTION in respiratory control is the possible significance of neurohumoral factors such as acetylcholine. Indeed, in a broader aspect, the entire area of neurotransmitters in central synaptic transmission is still uncertain.[1–3]

Earlier experiments[4] have demonstrated a relationship between the enzyme acetylcholinesterase (AChE, true cholinesterase) in certain brain areas and the functioning of the central portion of a respiratory reflex arc. The present experiments were undertaken to examine in greater detail the acetylcholine–acetylcholinesterase–choline acetylase (ACh-AChE-ChA) system and its relationship to respiratory control. Thus, these investigations were aimed at the following questions: first, what is the correlation, if any, between the components of this ACh-AChE-ChA system within certain brain areas and the magnitude of a respiratory reflex response (elicited by stimulation of Hering's nerve) when potentiated or inhibited by an anticholinesterase? And, second, having used an anticholinesterase (tetraethylpyrophosphate, TEPP) to produce fluctuations in the respiratory reflex and AChE activity,[4] what would be the effect of reversing the inhibition of the acetylcholinesterase activity, that is, administering compounds such as the oximes (pyridine-2-aldoxime methiodide, PAM), which reactivate AChE activity after it has been inhibited under certain conditions? Finally, are there critical thresholds or levels of ACh, AChE, or ChA in brain areas for inhibition or potentiation of a respiratory reflex, and, if so, is this uniform throughout the brain at various stages of reflex activity?

METHODS

The study was made on 211 anesthetized dogs of both sexes, weighing 8 to 17 kg.

Physiologic. Potentiation and inhibition of the reflex was accomplished by injecting varying doses of the anticholinesterase TEPP, and the central nervous system structures analyzed were ones that might directly or indirectly be concerned in respiratory control—the medulla, pons, temporal cerebral cortex,[5] and mesencephalon.[6] During eupneic breathing, Hering's nerve was excited by electrical stimuli, standardized as to strength, shock duration, frequency, duration of volley, and time interval between volleys, while minute volume of breathing was recorded, a method previously reported.[7,8]

The series of experiments can be outlined as follows:

Experimental Series I—TEPP plus saline. Suitable steady state control values of the reflex response were obtained, after which varying doses of TEPP (in 0.1 to 0.4 cc. of physiologic saline) were introduced via cisternal puncture. After a twenty-minute interval, physiologic saline was administered in 5 injections of 0.3 cc., each given three minutes apart. After an additional one hundred and twenty minutes after the first saline injection, the animals were killed at the one hundred and forty minute mark by bleeding from the aorta. The respiratory reflex response was measured just before, and the brain parts were removed and immersed instantly in liquid nitrogen. This is the primary experimental series, comprising 40 animals, with which all oxime-injected animals are to be compared.

From the Department of Physiology, Medical College of South Carolina, Charleston.

This work was supported by Grant B-954(C2) from the National Institute of Neurological Diseases and Blindness. Read before the Section of Neuropharmacology at the twelfth annual meeting of the American Academy of Neurology, Miami, April 1960.

Experimental Series II—TEPP plus oximes. Same as Series I except oximes were substituted for saline after TEPP to determine the effect of reactivation of AChE after alkyl phosphate inhibition. PAM (pyridine-2-aldoxime methiodide) was administered to 36 animals, P2S (2-hydroxyiminomethyl-N-methylpyridinium methanesulphonate) to 38, and DAM (diacetyl monoxime) to 8 animals.

Control Series III. The method consists of substituting physiologic saline solutions buffered to the *p*H of TEPP and the oximes (PAM, DAM, and P2S) to determine the influence of the volume of the various intraventricular injections as well as the effect of the *p*H of the drugs on the reflex response and on the central nervous system tissue analyses (23 animals).

Control Series IV. The primary purpose of testing this group was to ascertain the influence of the oxime itself on the reflex response and on the brain tissue analyses (10 animals).

In the 4 series, all injections were administered via cisternal puncture and the drugs were freshly prepared before administration. The carotid arterial blood pressure was recorded with a mercury manometer. In order to produce varying degrees of potentiation or inhibition of the respiratory reflex, triply distilled TEPP, ranging from 0.001 to 0.18 mg. per kilogram, was introduced directly onto the floor of the fourth ventricle, through polyethylene tubing.

The oxime PAM dosage was 5 mg. per kilogram. Though larger doses were desirable, the solubility of the compound (4 to 5%) limited the amount that could be introduced intracisternally. The oxime DAM dosage was 5 mg. per kilogram. Since the oxime P2S is highly soluble in water,[9] doses larger than above were administered initially. However, with doses over 5 mg. per kilogram, there were striking respiratory reactions of gasping, irregular, and periodic breathing which necessitated a reduction of the dosage to 5 mg. This may be a species problem, as suggested by Davies and Willey,[10] in which the dog has been shown to be highly sensitive to P2S.

One side of the brain was analyzed for AChE activity and the contralateral half for ACh studies. Other dogs supplied the sections for analyses of choline acetylase studies.

Biochemical analyses. *AChE activity* – the brain samples were analyzed for AChE activity by the titrimetric technic of Aprison, Nathan, and Himwich.[11] All analyses were done in triplicate, and the enzyme activity was calculated as milliequivalents per milligram of wet tissue per minute.

Total ACh—the method for measuring total ACh was that described by Stone,[12] namely, extraction with acidulated alcohol. The extracts were assayed on the frog rectus abdominis, and the total ACh was calculated as micromoles per kilogram.

Choline acetylase—the technic for determining the ChA activity in the brain tissue was identical with that employed by Hebb and Smallman,[13] using extracts of acetone-dried brain. These extracts were assayed on the frog rectus abdominis according to the method of Feldberg and Hebb,[14] and the ACh synthesis was expressed as micrograms per gram of fresh brain per hour.

Since many anesthetics exhibit some degree of anticholinesterase activity[15] and similarly affect ACh levels, a series of preliminary experiments were essential to ascertain the status of the anesthetic in these investigations. The anesthetic used was morphine sulphate (2.5 mg. per kilogram, subcutaneously) and urethane (1 gm. per kilogram, intraperitoneally). Previous work indicates that urethane itself has only slight anticholinesterase activity[15] but might influence ACh levels.[16] It is also well known that morphine acts as an anticholinesterase, although the concentrations for this action are very high[17] and earlier work indicates that a dosage 60% greater (4 mg. per kilogram) produced no significant effect with regards to AChE activity,[4] though again it might affect the ACh concentrations. Therefore, a series of experiments were undertaken to determine the effect of the morphine-urethane anesthetic on the AChE-ACh-ChA system under the conditions of the experiment.

The method of Crossland[18] was followed. In order to obtain the AChE-ACh-ChA values of the brain areas in unanesthetized dogs, the animals were immobilized with mephenesin (100 mg. per kilogram, intraperitoneally) and were killed at the onset of paralysis. Although mephenesin paralyzes by central action, it has no apparent effect on the ACh content of the

Effects of Anesthetic (Morphine-Urethane) on Acetylcholine (ACh), Acetylcholinesterase (AChE), and Choline Acetylase (ChA) in Cerebral Cortex, Medulla, Midbrain, and Pons

	Cerebral cortex	*Medulla*	*Midbrain*	*Pons*
	AChE activity			
	Group I (mephenesin) minus Group II (mephenesin + morphine-urethane)			
% difference	− 3.4	− 6.6	− 4.8	− 7.6
P	> 0.1	> 0.05	> 0.1	> 0.1
	Total ACh			
	Group II (mephenesin + morphine-urethane) minus Group I (mephenesin)			
% difference	+41.2	+50.5	+48.2	+44.0
P	< 0.01	< 0.01	< 0.01	< 0.01
	ChA activity			
	Group III (mephenesin) minus Group IV (mephenesin + morphine-urethane)			
% difference	− 9.4	− 7.5	− 5.7	− 9.8
P	< 0.05	< 0.05	> 0.05	< 0.05

brain if the animals are killed at the onset of paralysis.[18] The dogs were divided into 4 groups (6 in each group): Group I—mephenesin series (AChE and ACh); Group II—mephenesin + morphine-urethane (AChE and ACh); Group III—mephenesin series (ChA); Group IV—mephenesin + morphine-urethane (ChA).

RESULTS

Anesthesia series. The effects of the anesthetic (2.5 mg. of morphine sulfate per kilogram and 1 gm. of urethane per kilogram) are summarized in the table.

The AChE activity of the brain parts were 3 to 8% lower in Group II (mephenesin and morphine-urethane) than in Group I (mephenesin), but in all instances the differences were not significant. The total ACh concentrations were 41 to 51% greater in Group II than in Group I, and the differences were highly significant. The ChA activities of the brain areas were 6 to 10% lower in Group IV (mephenesin + morphine-urethane) than in Group III (mephenesin) in the pons, medulla, and cerebral cortex, and the differences were significant.

Reflex series. In the control group of 11 animals (the dogs receiving saline buffered to the *p*H of TEPP + the oximes, respectively), the respiratory reflex was +8.1% (± 6.23 standard error of mean).

Small doses of TEPP (0.001 to 0.0014 mg. per kilogram) promptly produced a characteristic hyperpnea plus a marked potentiation of the respiratory reflex (an increase from +62 to +140%). Larger doses (0.012 to 0.18 mg. per kilogram) caused a slight potentiation of the reflex (0 to +43%) at the lower end of the dosage scale, but, as the TEPP concentration was increased, there was a marked depression (up to −95%) of the reflex and, as the dosage was increased even further, a precipitous fall occurred in both the spontaneous and reflex breathing, which culminated in respiratory failure.

In all instances, the relationship among the reflex, the AChE activities, and the ACh concentrations in the brain areas examined followed a similar pattern, as is evident in Figures 1 (pons) and 2 (medulla), with the midbrain and the cerebral cortical graphs being similar in outline.

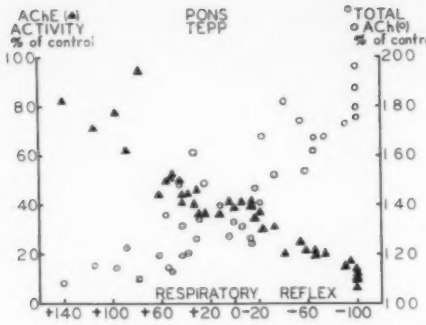


Fig. 1. Graph showing relationship between acetylcholinesterase (AChE = ▲) activity level and total acetylcholine (ACh = ○) concentration in pons (data expressed as percentage of control) and respiratory reflex response (expressed in percentage potentiation or inhibition) as a result of TEPP plus saline administration. Control level of AChE = 100; control level of ACh = 100. (Each point = 1 dog)

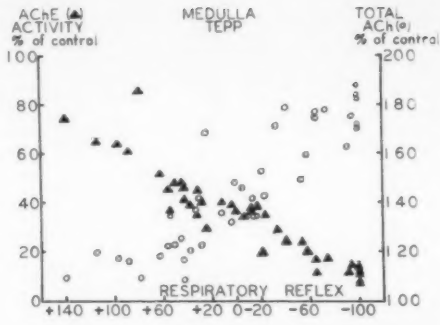


Fig. 2. Graph showing relationship between acetylcholinesterase (AChE = ▲) activity level and total acetylcholine (ACh = ○) concentration in medulla (data expressed as percentage of control) and respiratory reflex response (expressed in percentage potentiation or inhibition) as a result of TEPP plus saline administration. Control level of AChE = 100; control level of ACh = 100. (Each point = 1 dog)

TEPP plus saline series (40 animals). There is a progressive decline in the AChE activity levels with a decreasing reflex response coincident with a gradual increasing total ACh concentration after the administration of various doses of TEPP (Figs. 1 and 2).

TEPP plus PAM series (36 animals). This produced a shift in the curve to the right, indicating increasing levels of AChE activity (Figs. 3 and 4) paralleling the TEPP series. Concomitant with the increase in AChE activity, there is a shift in the curve toward decreased ACh concentrations, also paralleling the TEPP series (Figs. 5 and 6). The PAM itself produced no detectable change in the reflex, AChE activity, or ACh concentration.

TEPP plus P2S series (38 animals). This produced reactions similar to those observed with TEPP plus PAM, namely, a shift in the curve toward increased AChE activity levels, with corresponding decreased ACh concentrations. The P2S (5 mg. per kilogram) produced an increase in respiration for a period of twenty to sixty minutes. For a brief period, there was a gasping type of respiratory pattern. The P2S itself produced responses that were similar.

TEPP plus DAM series (8 animals). No significant changes were noted. All the experimental values of AChE and ACh fell within the controls.

Choline acetylase activities (32 animals). No significant differences were evident in the ChA activities between the controls and the experimental series.

After injection of TEPP, there was a rise in the blood pressure of 32 ± 7 mm. Hg. The oximes (PAM and P2S) failed to produce any reversal of this hypertension.

DISCUSSION

Anesthesia series. With the morphine-urethane anesthesia, there is a small depression of ChA activity in the cerebral cortex, medulla, and pons. Analogous results have been obtained by de la Lande and Bentley[19] on brain slices with morphine; however, this inhibitory effect on ACh synthesis is not specific for this enzyme since it cannot be obtained with extracted ChA. The ACh concentration in the anesthetized group was 41 to 51% higher than that in the unanesthetized series. This is in harmony with the results of Elliott, Swank, and Henderson[20] and Crossland[16] that the ACh of the brain rises during anesthesia.

Reflex series. An examination of the results

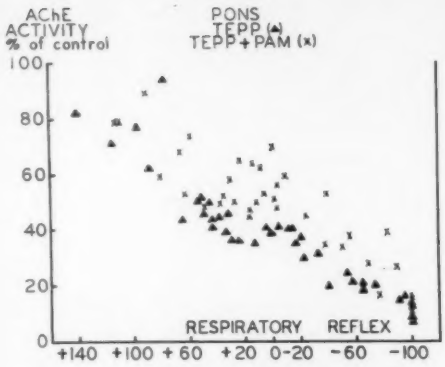


Fig. 3. Graph showing relationship between acetylcholinesterase (AChE = ▲) activity level after administration of TEPP plus saline and AChE activity level after addition of the oxime PAM (TEPP + PAM = X) in pons (data expressed as percentage of control) and respiratory reflex response (expressed in percentage potentiation or inhibition). Control level of AChE = 100. (Each point = 1 dog)

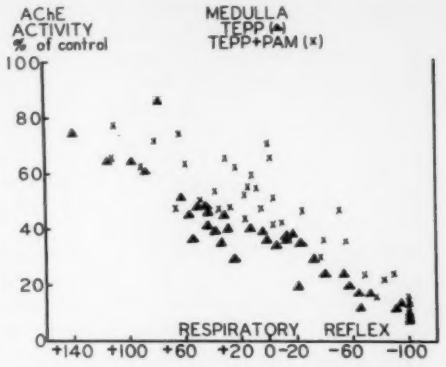


Fig. 4. Graph showing relationship between acetylcholinesterase (AChE = ▲) activity level after administration of TEPP plus saline and AChE activity level after addition of the oxime PAM (TEPP + PAM = X) in medulla (data expressed as percentage of control) and respiratory reflex response (expressed in percentage potentiation or inhibition). Control level of AChE = 100. (Each point = 1 dog)

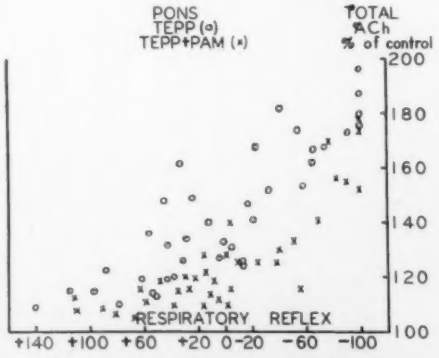


Fig. 5. Graph showing relationship between total acetylcholine (ACh = ○) concentration after administration of TEPP plus saline and ACh concentration after addition of the oxime PAM (TEPP + PAM = X) in pons (data expressed as percentage of control) and the respiratory reflex response (expressed in percentage potentiation or inhibition). Control level of ACh = 100. (Each point = 1 dog)

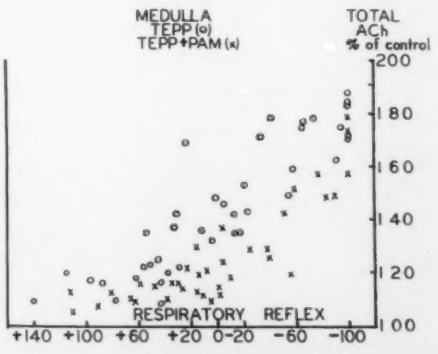


Fig. 6. Graph showing relationship between total acetylcholine (ACh = ○) concentration after administration of TEPP plus saline and ACh concentration after addition of the oxime PAM (TEPP + PAM = X) in medulla (data expressed as percentage of control) and respiratory reflex response (expressed in percentage potentiation or inhibition). Control level of ACh = 100. (Each point = 1 dog)

indicates that, after a marked potentiation of the reflex maximal at AChE values between 75 to 95% of the controls, there is a gradual but progressive decline in the AChE activities of the brain areas vitally concerned with respiration which parallels the fall in the potentiated respiratory reflex. Potentiation is still evident when the enzyme activities have dropped to 35 to 40% of the control values. This increased respiratory reflex response is a product of an abnormal accumulation of endogenous ACh as a result of inhibition of AChE activity by TEPP rather than any increased synthesis of ACh, since the ChA activity changes were not significant; this is in accord with Hebb's finding[21] that TEPP does not affect ChA activity. On this basis, it would be necessary to postulate also that accumulation of ACh beyond an optimum concentration results in a diminishing reflex response, since, after an initial marked increase, there is a declining potentiation in the reflex. Further, since with increasing ACh accumulation, corresponding to low AChE values, the reflex is decreased below normal, the possibility appears that the declining response is due to an inhibitory action of the accumulating ACh acting in opposition to its postulated excitatory effect.

This "dual action" concept of acetylcholine receives substantiation from the work of Duke, Pickford, and Watt[22] in which stimulation of the supraoptic nucleus of the dog (as measured by antidiuretic hormone release) occurred after administration of ACh and the anticholinesterase diisopropylfluorophosphate directly into the nucleus. On the other hand, Feldberg and Sherwood[23] demonstrated the inhibitory action of ACh by producing a "catatonic-like" stupor in a conscious cat when ACh and anticholinesterases were introduced into the lateral ventricles in the region of the periventricular gray matter. Thus, as Crossland postulates,[1] a relatively small increase will convert a stimulating dose of ACh into a paralyzing one.

Previously, Gesell, Hansen, and Worzniak[24] had demonstrated that ACh produced hyperactivity of the respiratory center in dogs when injected intraarterially or applied to the fourth ventricle and that the effect was graded in relation to the supposed concentration of ACh at the center. The respiratory failure observed is probably due to excessive accumulation of ACh which results in central depression, as surmised by Wright.[25] Respiratory failure was evident when the AChE activity was 7 to 14% of the control values. These results accord well with those of Bullock and associates,[26] who demonstrated the loss of action potential when the AChE dropped below a level of 17% of normal, and, similarly, Nachmansohn and Feld[27] have indicated that death occurs when the total AChE activity is 10% of normal or less.

Marked inhibition of the reflex appeared when the AChE activity levels reached a range of approximately 12 to 21% of the controls. One might speculate, as regards to this particular reflex, whether a fall of this magnitude is essential before marked depression can occur, for White[28] has shown that in rabbits the AChE activity of 1 of the 2 caudate nuclei must be reduced at least 40% of the control value before forced circus movements in the rabbit are to be expected.

The ACh levels generally remained +10 to +50% greater than the controls without any evidence of inhibition of the reflex. At the onset of reflex inhibition, the ACh concentrations were usually greater than 50%, reaching a peak during respiratory failure of +70 to +120% above the control values. Therefore, it is apparent that a relatively high level of ACh concentration is necessary before marked inhibition of this reflex is attainable. Coincident with the inhibition of the AChE, there is an accumulation of ACh in these brain areas, which is correlated with the functioning of the central portion of a respiratory reflex arc. Therefore, one can assume that these events are intimately related to one another and are of importance in the process of respiratory control.

The effect of the combination of the TEPP + oximes (PAM, P2S) indicates a small but statistically significant shift in the curve which provides a reactivation of the AChE that has been inhibited by TEPP. Is this small but significant shift important? Koelle[29] found that PAM regenerates AChE on the external surfaces of mammalian ganglion cells. Holmstedt[30] emphasizes the fact that, although the external surfaces make up only a small part of the total AChE of the ganglion, it is the fraction which limits the access of the locally re-

leased or systemically circulating acetylcholine to the sensitive area of the cell surfaces. Therefore, the reactivation of a comparatively small percentage of the total AChE of a tissue may be of great significance to the function of that particular tissue. This takes on added meaning when one observes the ACh concentrations from the contralateral sections of the brain, in which there is an analogous curve showing decreased ACh concentrations. The oxime experiments indicate that, with a shift in the AChE activities and ACh concentrations, a relationship to the respiratory reflex is still evident. However, the evidence does not deny the existence of other factors which are presumably inherent in a process as complex as respiratory control, but these investigations do suggest that a cholinergic factor may play some active role in respiratory reflex activity under the conditions of the experiment.

Oxime reactivation of AChE occurs in vivo in the blood,[31,32] motor end plates,[29] and diaphragm[33] after poisoning with organophosphates. Similarly, in vitro oxime (PAM) regeneration of whole brain AChE occurs just as readily as in the tissues previously mentioned,[33,34] but in vivo reactivation is small[32] or absent.[31,34-36] Wills and Borison[37] have shown that PAM failed to lower the voltage threshold for electrical stimulation of a medullary inspiratory site after it had been elevated by sarin, thus manifesting a low degree of effectiveness in the oxime reactivation of AChE within the central nervous system after organic phosphate poisoning.

It has been suggested, however, that the oxime PAM, due to its chemical configuration, does not penetrate the "blood-brain barrier" readily.[34,38] Corroboration of this hypothesis is supported by the experiments of Kewitz and Nachmansohn[34] in which smaller concentrations of PAM resulted in no effect on brain AChE reactivation in vivo but higher concentrations produced reactivation of the brain AChE, at a level of 25% higher than that expected without the PAM. Additional confirmatory evidence of the slow penetration of PAM through the "blood-brain barrier" in rabbits and in man is presented by Jager and associates.[39]

In the work mentioned previously, the oximes were administered intravenously, intramuscularly, or intraperitoneally. Thus, in the present investigations, in which the "blood-brain barrier" is bypassed by administering the PAM via cisternal puncture, the slow penetration of PAM into the central nervous system observed by the previous workers is now avoided.

Moreover, Rosenberg[40] found that PAM caused a significant increase in the AChE level in the cerebral cortex and cerebellum, plus a marked rise in the medulla and pons including the region of area postrema of the rabbit. The data show that sufficient amounts of PAM are able to penetrate the brain, reactivating significant amounts of inhibited enzyme after alkyl phosphate poisoning. Recently, Brown[41] demonstrated that, when P2S was administered intracisternally, it did not alter the central effects produced by fatal doses of the anticholinesterase sarin. The present investigations are in agreement with these findings, for, when the organophosphate poisoning is too severe, the oximes PAM and P2S did indeed fail to reverse the marked reflex inhibition or respiratory failure. It is when the TEPP doses are at sublethal levels that there is a small but significant shift in the AChE activities and ACh concentrations with a corresponding change in the respiratory reflex activity.

Though the results obtained in these investigations are compatible with a cholinergic factor in the central nervous control of breathing, they do not by themselves constitute conclusive proof of such a mechanism. Several crucial points remain to be developed.

Feldberg and Vogt[42] have presented evidence that there is a frequent alternation of cholinergic and noncholinergic neurons in afferent and efferent pathways within the central nervous system. Thus, even though there is strong suggestive evidence that ACh is a transmitter within widely scattered synapses in the central nervous system, the nature and identity of the possible transmitter in the noncholinergic components is still undetermined.[1-3]

In addition, since chemical compounds may affect areas of the brain in diverse ways, experiments concerning the vital role of critical changes in the enzymes and neurotransmitters

at selective loci within the brain are required.

Finally, the problem of anesthesia urgently requires attention. In the present studies, the base levels of AChE and ChA activities for the anesthetized control animals are at a significantly different level than that of the unanesthetized dog. However, due to the very nature of these experiments, it is obviously essential to utilize anesthetic agents, but Holmstedt[30] directs attention to the fact that the anesthetics may disguise the symptoms and effects of the anticholinesterases and may lead to erroneous conclusions, for the activity of many brain areas is suppressed to some degree by their usage.

SUMMARY

1. A study was made on 211 anesthetized dogs to examine the relationship of the components of the acetylcholine–acetylcholinesterase–choline acetylase (ACh-AChE-ChA) system within the brain with the magnitude of a respiratory reflex response. The latter reflex was elicited by stimulation of Hering's nerve, and potentiation and inhibition of the reflex was obtained by administering varying doses of the alkyl phosphate, tetraethylpyrophosphate (TEPP), via cisternal puncture.

2. A significant correlation exists between the respiratory reflex and the ACh and AChE in the cerebral cortex, midbrain, pons, and medulla. With a decreasing respiratory reflex, there is a gradual decline in the AChE activities in the brain areas, accompanied by a corresponding progressive increase in the total ACh concentrations in these areas. Small levels of ACh were associated with potentiation of the reflex, whereas elevated levels of ACh produced marked inhibition of the reflex which culminated in respiratory failure. However, no correlation was evident between the ChA activities and the respiratory reflex responses.

3. The oximes, pyridine-2-aldoxime methiodide (PAM) and 2-hydroxyiminomethyl-N-methylpyridinium methanesulphonate (P2S), were utilized to reactivate the AChE after it had been inhibited by TEPP, which resulted in correspondingly decreased ACh concentrations but with the relationship to the reflex still evident.

4. The evidence does not deny the existence of other factors which are presumably inherent in a process as complex as respiratory control, but these investigations do suggest that a cholinergic factor may play some active role in central respiratory reflex activity.

REFERENCES

1. Crossland, J.: Chemical transmission in the central nervous system. J. Pharm. & Pharmacol. 12:1, 1960.
2. Elkes, J.: Effects of psychosomimetic drugs in animals and man. In Abramson, H. A., ed.: Neuropharmacology, Tr. Third Josiah Macy, Jr., Foundation Conference. Madison, N. J., Madison Printing Co., 1957, p. 205.
3. Giarman, N. J.: Neurohumors in the brain. Yale J. Biol. & Med. 32:73, 1959.
4. Metz, B.: Brain acetylcholinesterase and a respiratory reflex. Am. J. Physiol. 192:101, 1958.
5. Kaada, B. R.: Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of rhinencephalic and other structures in primates, cat and dog. Acta physiol. scandinav. (supp. 83) 24:262, 1951.
6. Baxter, D. W., and Olszewski, J.: Respiratory responses evoked by electrical stimulation of pons and mesencephalon. J. Neurophysiol. 18:276, 1955.
7. Metz, B., and Bernthal, T. G.: Interaction of respiratory drives. Fed. Proc. 12:99, 1953.
8. Metz, B.: A respiratory reflex as affected by an anticholinesterase. Am. J. Physiol. 185:142, 1956.
9. Creasey, N. H., and Green, A. L.: 2-hydroxyiminomethyl-N-methylpyridinium methanesulphonate (P2S), an antidote to organophosphorus poisoning. Its preparation, estimation and stability. J. Pharm. & Pharmacol. 11:485, 1959.
10. Davies, D. R., and Willey, C. L.: The toxicity of 2-hydroxyiminomethyl-N-methylpyridinium methanesulphonate (P2S). Brit. J. Pharmacol. 13:212, 1958.
11. Aprison, M. H., Nathan, P., and Himwich, H. E.: Brain acetylcholinesterase activities in rabbits exhibiting 3 behavioral patterns following intracarotid injection of di-isopropyl fluorophosphate. Am. J. Physiol. 177:175, 1954.
12. Stone, W. E.: Acetylcholine in the brain. I. "Free," "bound," and total acetylcholine. Arch. Biochem. 59:181, 1955.
13. Hebb, C. O., and Smallman, B. N.: Intracellular distribution of choline acetylase. J. Physiol. 134:385, 1956.
14. Feldberg, W., and Hebb, C. O.: The effects of magnesium ions and of creatine phosphate on the synthesis of acetylcholine. J. Physiol. 106:8, 1947.
15. Augustinsson, K.: In Summer, J. B., ed.: The Enzymes. New York, Academic Press, 1950, Vol. 1, Part I, Ch. 10.
16. Crossland, J.: Brain acetylcholine during hypoglycemia, anoxia, and anesthesia. In Proc. Third International Congress of Biochemistry, Brussels, C. Liebecq, ed. New York, Academic Press, Inc., 1956, p. 507.
17. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics. 2d ed. New York, Macmillan, 1955, Ch. 13.
18. Crossland, J.: The use of liquid air in the extraction of acetylcholine. J. Physiol. 114:318, 1951.
19. de la Lande, I. S., and Bentley, G. A.: The addition of morphine and antagonists of the narcotic action of morphine on acetyl choline synthesis in brain. Australian J. Exper. Biol. & M. Sc. 33:555, 1955.
20. Elliott, K. A. C., Swank, R. L., and Henderson,

N.: Effects of anesthetics and convulsants on acetylcholine content of brain. Am. J. Physiol. 162:469, 1950.
21. Hebb, C. O.: Biochemical evidence for the neural function of acetylcholine. Physiol. Rev. 37:196, 1957.
22. Duke, H. N., Pickford, M., and Watt, J. A.: The immediate and delayed effects of diisopropylfluorophosphate injected into the supraoptic nuclei of dogs. J. Physiol. 111:81, 1950.
23. Feldberg, W., and Sherwood, S. L.: Behaviour of cats after intraventricular injections of eserine and DFP. J. Physiol. 125:488, 1954.
24. Gesell, R., Hansen, E. T., and Worzniak, J. J.: Humoral intermediation of nerve cell activation in the central nervous system. Am. J. Physiol. 138:776, 1943.
25. Wright, P. G.: An analysis of the central and peripheral components of respiratory failure produced by anticholinesterase poisoning in the rabbit. J. Physiol. 126:52, 1954.
26. Bullock, T. H., Grundfest, H., Nachmansohn, D., and Rothenberg, M. A.: Effect of di-isopropyl fluorophosphate (DFP) on action potential and cholinesterase of nerve. J. Neurophysiol. 10:63, 1947.
27. Nachmansohn, D., and Feld, E. A.: Studies on cholinesterase. IV. On the mechanism of di-isopropyl fluorophosphate action in vivo. J. Biol. Chem. 171:715, 1947.
28. White, R. P.: Relationship between behavioral changes and brain cholinesterase activity following graded intracerebral injections of DFP. Proc. Soc. Exper. Biol. & Med. 93:113, 1956.
29. Koelle, G. B.: Histochemical demonstration of reactivation of acetylcholinesterase in vivo. Science 125: 1195, 1957.
30. Holmstedt, B.: Pharmacology of organophosphorus cholinesterase inhibitors. Pharmacol. Rev. 11:567, 1959.
31. Hobbiger, F.: Protection against the lethal effects of organophosphates by pyridine-2-aldoxime methiodide. Brit J. Pharmacol. 12:438, 1957.
32. Rutland, J. P.: The effect of some oximes in sarin poisoning. Brit. J. Pharmacol. 13:399, 1958.
33. Kewitz, H.: A specific antidote against alkyl phosphate intoxication. III. Repair of a chemical lesion. Arch. Biochem. 66:263, 1957.
34. Kewitz, H., and Nachmansohn, D.: A specific antidote against lethal alkyl phosphate intoxication. IV. Effects in brain. Arch. Biochem. 66:271, 1957.
35. Hobbiger, F., and Sadler, P. W.: Protection against lethal organophosphate poisoning by quaternary pyridine aldoximes. Brit. J. Pharmacol. 14:192, 1959.
36. Sanderson, D. M., and Edson, E. F.: Oxime therapy in poisoning by six organophosphorus insecticides in the rat. J. Pharm. & Pharmacol. 11:721, 1959.
37. Wills, J. H., and Bonison, H. L.: In recent studies of organic phosphate poisoning by J. H. Wills. Fed. Proc. 18:1020, 1959.
38. Davies, D. R., and Green, A. L.: The chemotherapy of poisoning by organophosphate anticholinesterases. Brit. J. Indust. Med. 16:128, 1959.
39. Jager, B. V., Stagg, G. N., Green, N., and Jager, L.: Studies on the distribution and disappearance of pyridine-2-aldoxime methiodide (PAM) and of diacetyl monoxime (DAM) in a man and in experimental animals. Bull. Johns Hopkins Hosp. 102:225, 1958.
40. Rosenberg, P.: In Nachmansohn, D.: Chemical and Molecular Basis of Nerve Activity. New York, Academic Press, 1959, p. 134.
41. Brown, R. V.: The effects of intracisternal sarin and pyridine-2-aldoxime methyl methanesulphonate in anesthetized dogs. Brit. J. Pharmacol. 15:170, 1960.
42. Feldberg, W., and Vogt, M.: Acetylcholine synthesis in different regions of the central nervous system. J. Physiol. 107:372, 1948.

Role of the sympathetic nervous system in urinary bladder function in the cat

Everett H. Ingersoll, Ph.D., Louise L. Jones,
and Erling S. Hegre, Ph.D.

IN HIS CLASSIC STUDIES on the function of the urinary bladder, Elliott[1] demonstrated the antagonistic action of the sympathetic and parasympathetic systems. He showed that the sacral outflow, when stimulated, produced a sustained contraction of the detrusor muscle with inhibition of the internal sphincter, while excitation of the hypogastric nerves resulted in a contraction of the internal sphincter and the muscle at the base of the bladder, together with relaxation of the remainder of the vesical musculature. The extensive observations of Learmonth[2] in man and Langworthy[3] in the cat added to the strength of Elliott's views.

Other investigators have questioned the purely inhibitory action of the sympathetics on the detrusor muscle. MacDonald and McCrea[4] reported that the response of the bladder to hypogastric nerve stimulation was either excitatory or inhibitory, depending upon the condition of the muscle tonus and the depth of anesthesia. Then too, others[5–7] have found that stimulation of the sympathetic outflow in the cat and dog evoked a contraction, followed immediately by relaxation, which was not confined to the base of the bladder but extended to all portions of the vesical wall. A recent study[8] has shown also that the hypogastric nerves participate in both a vesical and a urethral contraction which were followed by a rapid drop in urethral resistance.

Bladder responses have been produced by electrical stimulation of forebrain structures by many investigators. These have been both excitatory and inhibitory in nature, which in the opinion of most of the workers[9–11] were mediated by the pelvic nerves. Others credited the effect obtained either to the area stimulated[12] or to the frequency of the electrical current supplied.[13,14] Wang and Harrison[15] observed contractions after section of the sacral roots in response to central stimulation. They reported that such responses were similar to those obtained after stimulation of hypogastric nerves and disappeared after severance of those nerves. They concluded that the bladder impulse was normally brought down from higher levels by both the sacral autonomic and sympathetic systems and that the contraction must then be the resultant effect.

In order to clarify the extent to which the sympathetic system participates in bladder activity, the present study was undertaken. This was done by comparing the responses obtained after electrical stimulation of points in the forebrain in the intact animal and after progressive denervation of the sympathetic and parasympathetic outflow to the bladder.

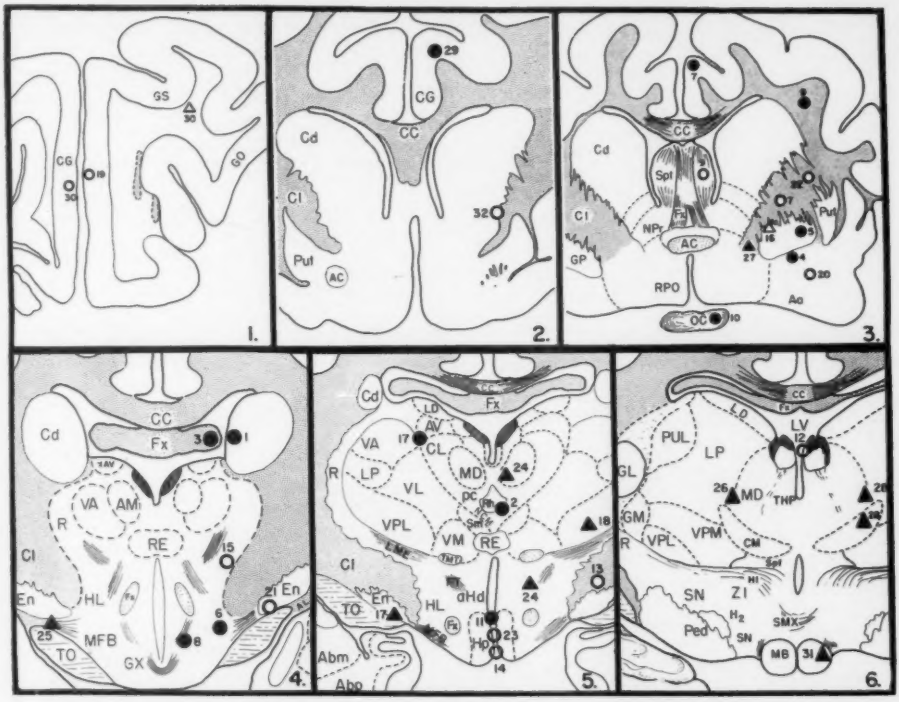
METHODS

The bladder responses in 46 adult cats were recorded after electrical stimulation of points in the forebrain, of which 32 were selected for inclusion in this report (Figs. 1 through 6). The animals were lightly anesthetized with intraperitoneal and intramuscular injections of chloralosane and Dial (Ciba). Minimal strength current was supplied by a Grass S4A model stimulator at frequencies ranging from 6 to 100 per second and with pulse durations of 5 to 10 milliseconds. In a few of the earlier experiments, a Harvard inductorium was used. Bipolar electrodes (constructed from 2 pieces

From the Department of Anatomy, Medical College of Virginia, Richmond.

This investigation was supported in part by Research Grant B-704 from the National Institute of Neurological Diseases and Blindness.

Read at the Section of Neuroanatomical Sciences of the twelfth annual meeting of the American Academy of Neurology, Miami Beach, April 28, 1960.



In Figures 1 through 6, abbreviations used are those employed by Jasper and Ajmone-Marsan[17] with the exception of the following: CG=gyrus cinguli; GO=gyrus orbitalis; GS=gyrus suprasylvanius; LV=ventriculus lateralis. Symbols for the designation of the type of bladder responses obtained are as follows: ●=sustained contraction; ○=unsustained contraction; ▲=inhibition of bladder rhythm together with relaxation of bladder musculature; △=relaxation of bladder musculature.

Fig. 1. Transverse section rostral to lateral ventricles and basal ganglia. Localization of points yielding bladder responses in cats 19 and 30

Fig. 2. Transverse section rostral to crossing of anterior commissure. Localization of points yielding bladder responses in cats 29 and 32

Fig. 3. Transverse section at level of crossing of anterior commissure. Localization of points yielding bladder responses in cats 4, 5, 7, 9, 10, 16, 20, 22, and 27

Fig. 4. Transverse section caudal to optic chiasm at level of Gasser's commissure. Localization of points yielding bladder responses in cats 1, 3, 6, 8, 15, 21, and 25

Fig. 5. Transverse section rostral to mammillary bodies. Localization of points yielding bladder responses in cats 2, 11, 13, 14, 17, 18, 23, and 24

Fig. 6. Transverse section at level of mammillary bodies. Localization of points yielding bladder responses in cats 12, 26, 28, and 31

TABLE 1

HYPOGASTRIC NERVE INFLUENCE IN SUSTAINED BLADDER CONTRACTIONS

Cat	*Peripheral innervation*	*Frequency per second*	*Point stimulated**	*Bladder response*
1	Intact	8	Cd-4	Vigorous contraction, short latency
	HS†	8		Augmented contraction
2	Intact	21	Rh-5	Moderate contraction, short latency
	HS	21		Augmented contraction
	HS, LPS	21		None
3	Intact	20	Fx-4	Vigorous contraction, short latency
	HS	20		Augmented contraction
	HS, LPS	20		None on left; slow contraction on right
4	Intact	20	GP, Aa-3	Prompt, vigorous contraction
	HS	20		Augmented contraction with slow relaxation
5	Intact	30	GP-3	Vigorous contraction, short latency
	HS	30		Unchanged
	HS	100		None
	HS	10		Slow but vigorous contraction, long latent period
	HS, LPS	10		Contraction diminished or abolished on left; unsustained contraction on right
6	Intact	30	HL-4	Prompt, vigorous contraction, slow relaxation
	HS	30		Unchanged
	HS, LPS	30		Contraction diminished or abolished on left; diminished on right
7	Intact	38	CG-3	Prompt, vigorous contraction
	HS	38		Relaxation on left; moderate, unsustained contraction on right
	HS, LPS	38		None on left; unsustained contraction on right
8	Intact	10	HL-4	Moderate contraction, short latency
	HS	10		None on right, diminished or abolished on left
9	Intact	25	CI-3	Moderate unsustained contraction, long latency
	Intact	100		Unchanged except for short latency
	Intact	6		Moderate sustained contraction
	HS	6		Weak, unsustained contraction
	HS	21	Spt-3	Unsustained contraction
10	Intact	20	OC-3	Vigorous contraction, long latency
	Intact	100		Augmented contraction
	LPS	20		None on left; vigorous, slow contraction on right
	LPS, RPS	20		None on left; slow contraction in a few areas on right

*Abbreviations used in this column in Tables 1 through 5 are those employed by Jasper and Ajmone-Marsan.[37] The number following the abbreviation refers to the text figure showing the exact placement of the stimulating electrode.

†Other abbreviations used in Tables 1 through 5: HS—hypogastric nerves sectioned; LPS—left pelvic nerves sectioned; RPS—right pelvic nerves sectioned; HI—Harvard inductorium

of nichrome wire insulated except at their tips) were oriented with the aid of a Horsley-Clarke stereotaxic apparatus.

Methods of observation and recording results have been described.[16] Intravesical pressures were maintained at levels ranging from 4 to 20 cm. H_2O and seemed to play no role in the type of response obtained. When a reactive point was located in the forebrain, several experiments were done employing different frequencies and progressive denervation of the bladder. Areas of the brain which had been explored were fixed in 10% formalin, sectioned, and stained, and the reactive points were identified.

RESULTS

The influence of the sympathetic outflow in sustained bladder contractions after stimulation of forebrain structures is summarized in Table 1. In some animals, section of the hypogastrics after a bladder response was obtained increased the vigor of the contraction and delayed the relaxation after cessation of stimulation (cats 1 through 4, Fig. 7). In others, such as cat 7 (Fig. 8), section of the hypogastrics often abolished the response with subsequent relaxation, greatly delayed the onset of contraction, or even changed the type of contraction. Section of the pelvic nerves on one side after division of the hypogastrics

Figures 7 through 10 are outline sketches of muscle activity taking place upon the exposed surface of the bladder in each of 12 areas (A1 through D2). Each circle represents activity during each second of observation. Onset of stimulation began with the first circle of each curve (indicated by arrow in Figure 9), cessation of stimulation by upward pointing arrow. A graph with an upward curve indicates muscle contraction, a downward curve, relaxation. Inserts: kymograph record of bladder volume during each observation; upstroke indicates diminution in volume.

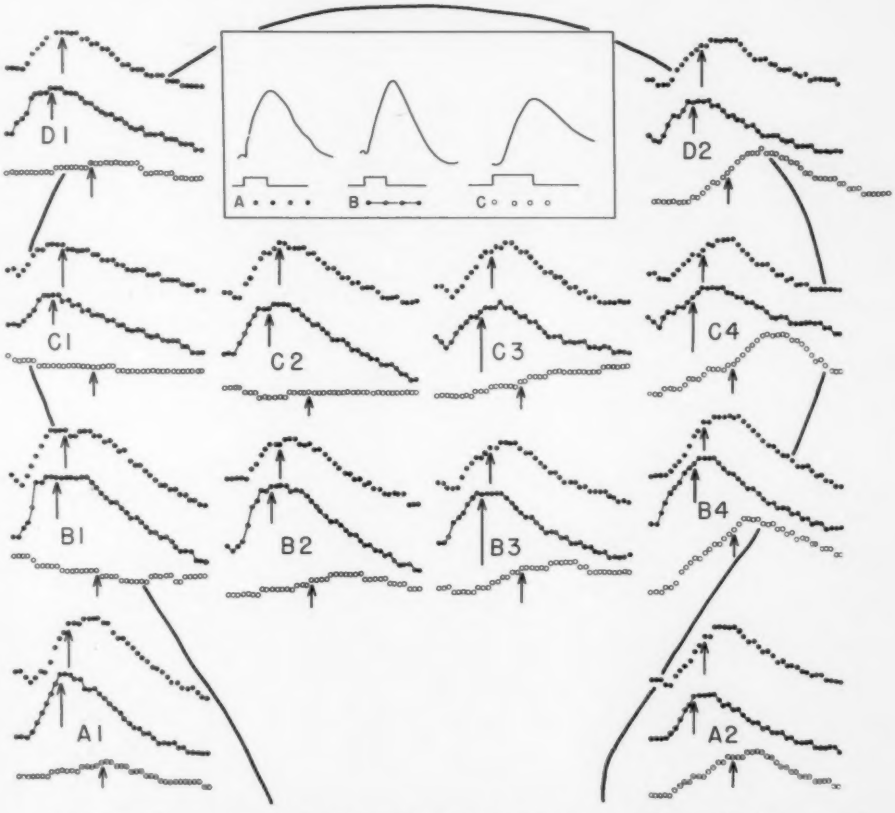


Fig. 7. Bladder responses in cat 3 after stimulation of fornix at a frequency of 20 per second and an intravesical pressure held constant at 13 cm. H_2O. [A] Upper graphs, intact nerves; [B] middle graphs, hypogastric nerves sectioned; [C] lower graphs, additional unilateral section pelvic nerves

often greatly altered the response, not only on the side of section of the pelvic nerves but on the opposite side as well (cats 2, 3, 5, 6, and 7). In cat 10, section of the pelvic nerves on both sides did not completely abolish the response.

In cats 12 through 15, forebrain stimulation evoked an unsustained type of contraction which was similar in many respects to that observed after stimulation of hypogastric nerves (Table 2). Section of the pelvic nerves altered but did not abolish the bladder response in this series of animals (see Fig. 9, cat 13).

The hypogastric nerve influence in inhibi-

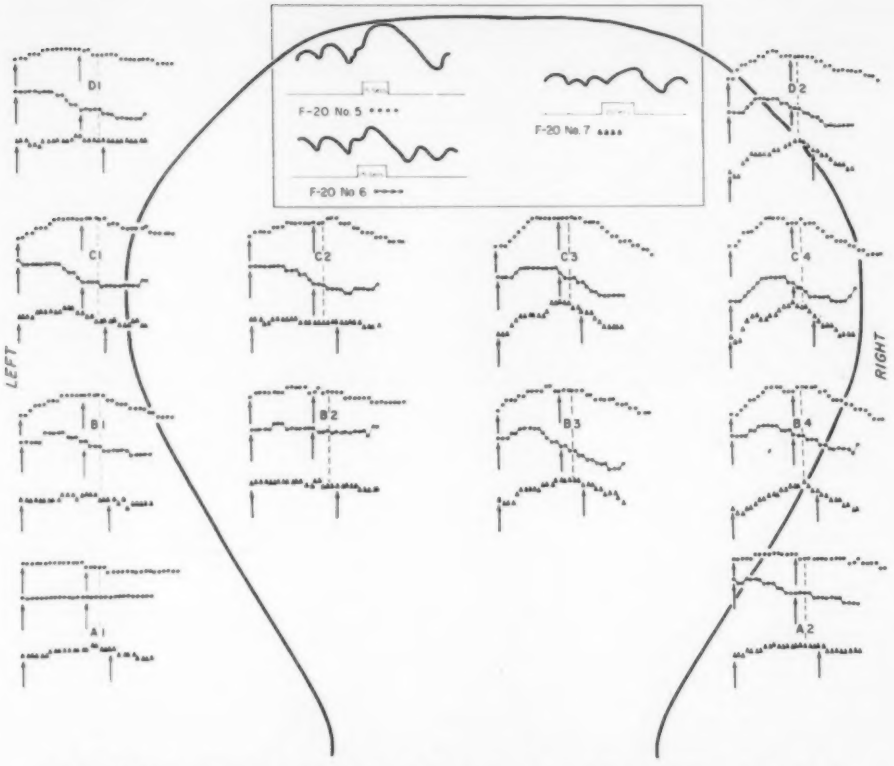


Fig. 8. Bladder responses in cat 7 after stimulation of a point in the cingular gyrus at a frequency of 38 per second and an intravesical pressure held constant at 10.5 cm. H_2O. Exp. 5 (upper graphs), intact nerves; Exp. 6 (middle graphs), hypogastric nerves sectioned; Exp. 7 (lower graphs), additional section left pelvic nerves

TABLE 2

HYPOGASTRIC NERVE INFLUENCE IN UNSUSTAINED BLADDER CONTRACTIONS

Cat	*Peripheral innervation*	*Frequency per second*	*Point stimulated*	*Bladder response*
12	Intact	HI	HbM-6	Moderate contraction, short latency
	LPS, RPS	HI		Weak contraction
13	Intact	HI	CI-5	Prompt, vigorous contraction
	LPS, RPS	HI		None in some areas; in others, weak with long latency
	LPS, RPS, HS	HI		Marked relaxation after cessation of stimulation
14	Intact	30	Hp-5	Weak contraction, long latency
	LPS, RPS	30		Some areas unchanged; none in other regions
15	Intact	HI	R-4	Prompt, vigorous contraction
	RPS, LPS*	HI		Augmented contraction (sustained in some areas)

*Autopsy revealed intact third sacral nerve on right, first and third sacrals on left.

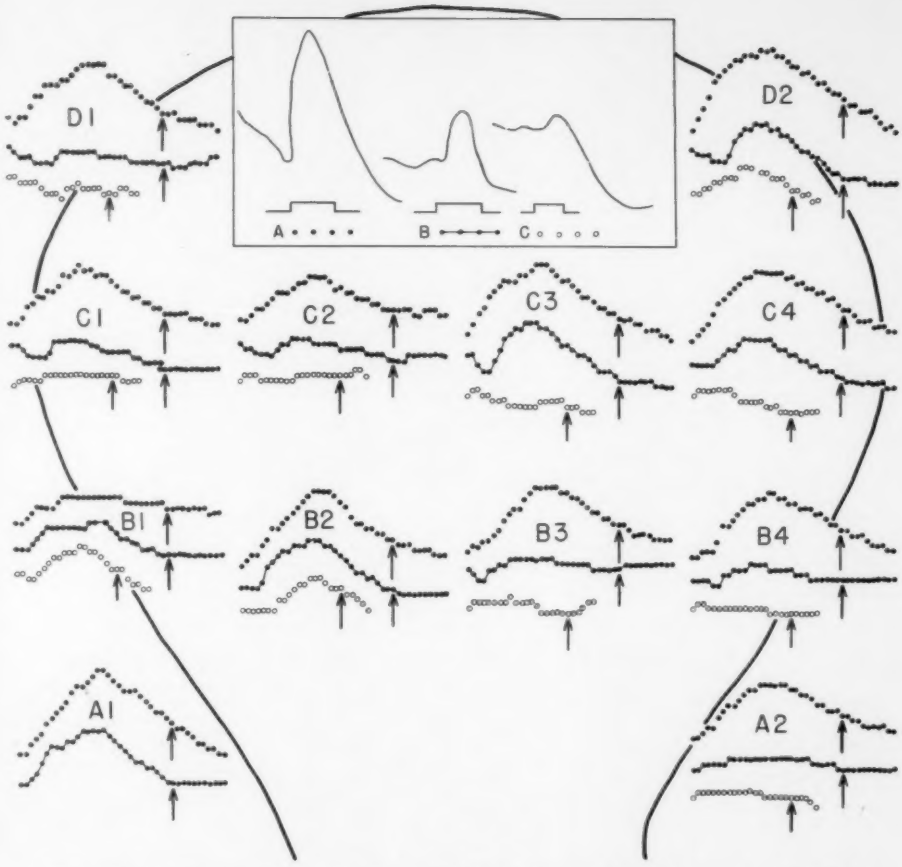


Fig. 9. Bladder responses in cat 13 after stimulation of internal capsule by means of a Harvard inductorium. Intravesical pressure not recorded. [A] Upper graphs, intact nerves; [B] middle graphs, pelvic nerves sectioned; [C] lower graphs, additional section of hypogastric nerves.

TABLE 3

HYPOGASTRIC NERVE INFLUENCE IN INHIBITORY BLADDER RESPONSES

Cat	*Peripheral innervation*	*Frequency per second*	*Point stimulated*	*Bladder response*
16	Intact	32	GP-3	Relaxation only
	Intact	100		None
	HS	32		Relaxation only
	HS, LPS	32		None
17	Intact	100	TO, En-3	Relaxation with inhibition of rhythm*
	Intact	6		None
	HS	100		Relaxation more pronounced
18	Intact	22	VPL-3	Relaxation with inhibition of rhythm
	HS	22		Augmented relaxation
	HS, LPS	22		None on left; weak relaxation on right

*Eight minutes previously, a sustained contraction was obtained from the same puncture line in the dorsal part of the thalamus at frequencies of 6 and 60 per second.

TABLE 4
PELVIC NERVE INFLUENCE IN UNSUSTAINED BLADDER CONTRACTIONS

Cat	*Peripheral innervation*	*Frequency per second*	*Point stimulated*	*Bladder response*
19	Intact	40	CG-1	Predominately right-sided moderate contraction
	LPS, RPS	40		None
20	Intact	30	Aa-3	Prompt, vigorous contraction, mostly on right
	RPS	30		None
21	Intact	21	En-4	Prompt, vigorous contraction
	HS	21		Unchanged
	HS, LPS	21		None in most areas on left; weak contraction on right
22	Intact	20	CI-3	Prompt, vigorous contraction
	Intact	100		None
	RPS	20		None on right; weak contraction on left
23	Intact	20	Hp-5	Prompt, vigorous contraction
	LPS, RPS	20		None

TABLE 5
PELVIC NERVE INFLUENCE IN INHIBITORY BLADDER RESPONSES

Cat	*Peripheral innervation*	*Frequency per second*	*Point stimulated*	*Bladder response*
24	Intact	20	HL-5	Relaxation with inhibition of rhythm
	HS	20	MD-5	Unchanged
	HS, LPS	20		Unchanged on right; diminished response on left
25	Intact	47	TO, En-4	Moderate relaxation on left
	HS	47		Unchanged
	HS, LPS	47		None
26	Intact	50	LP, MD-6	Marked relaxation with inhibition of rhythm
	HS	50		Unchanged
27	Intact	50	CI-3	Relaxation with inhibition of rhythm
	LPS, RPS	50		None
28	Intact	25	MD-6	Relaxation with inhibition of rhythm
	Intact	100		None
	Intact	22	CM-6	Relaxation with inhibition of rhythm
	LPS, RPS	22		None

tory bladder responses is shown in Table 3. Relaxation of the bladder musculature was noted in cat 16 after stimulation of the globus pallidus. Section of the hypogastrics had no effect on this response, but additional section of the pelvic nerves on one side abolished the response on both sides of the bladder. In cats 17 and 18, section of the hypogastrics seemed to augment the inhibitory response.

Impulses mediated by the pelvic nerves played a dominant role in a considerable number of unsustained and inhibitory bladder responses obtained after stimulation of structures in the forebrain (Tables 4 and 5 and Fig 10). The characteristic feature in this series of observations was that section of the hypogastrics had no effect upon the response, while division of the parasympathetic outflow invariably abolished the bladder activity.

DISCUSSION

In the present study 2 types of excitatory responses were observed; one of these was the sustained contraction, which had characteristics similar to that evoked by stimulation of parasympathetic bladder nerves.[18] In this type of response, there was usually a very short latent period (two to six seconds), the contraction rose to its maximum height in ten to twelve seconds, and relaxation did not occur until cessation of stimulation. Sustained contractions have been obtained by others* from the cortex,[19,20] amygdaloid nucleus,[21,22] hypothalamus,[10,12–14,23,24] internal capsules,[19] and preoptic area.[23] In the present study, points yield-

*Many other investigators have reported bladder contractions after forebrain stimulation, but, from their published descriptions, it was not possible to differentiate between sustained and unsustained contractions.

ing sustained contractions have been localized in the caudate, submedian, central median, and amygdaloid nuclei, fornix, internal capsule, optic chiasm, globus pallidus, and hypothalamus.

The second type of excitatory response was the unsustained, or hypogastric-like, contraction. This response, like the sustained contraction, had a short latent period and reached its maximum contraction in ten to twelve seconds, but, unlike the former response, the unsustained contraction relaxed rapidly to its initial level irrespective of the stimulus time.[16] Unsustained contractions have been reported from the cortex,[19] hypothalamus,[12,13,24] medial preoptic area,[14] and putamen.[14] In the present study, stimulation of the amygdaloid, entopeduncular, habenular, and reticular nuclei, internal capsule, hypothalamus, and cingular gyrus evoked unsustained contractions.

The results of most investigators are in agreement with those of Wang and Harrison,[15]

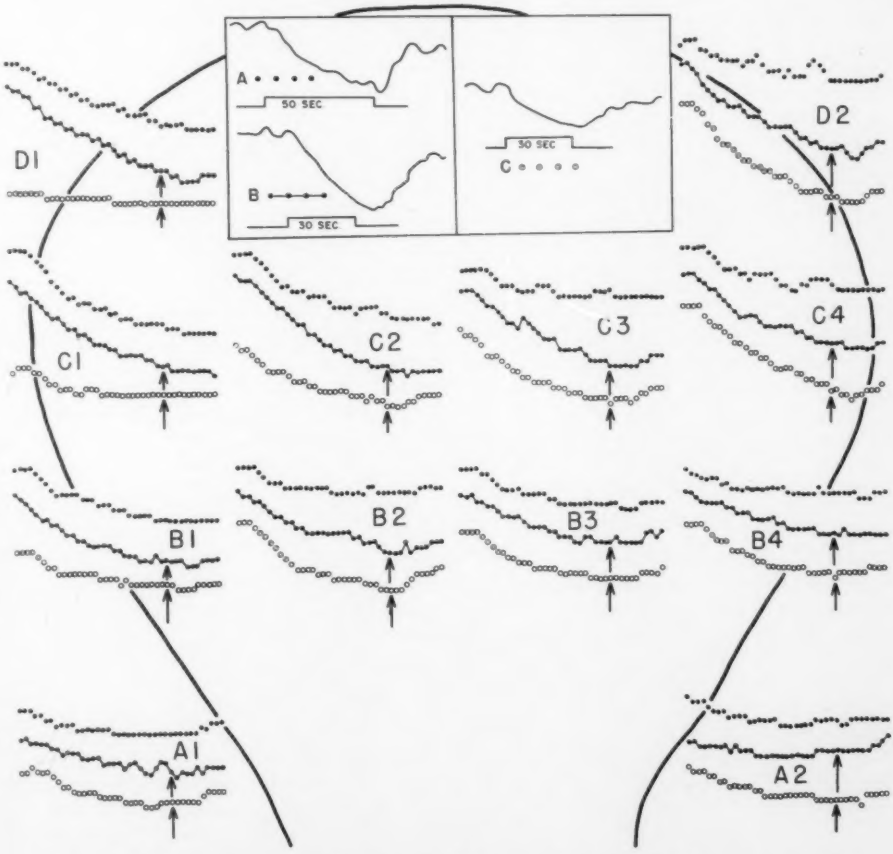


Fig. 10. Bladder responses in cat 24 after stimulation at a frequency of 20 per second and an intravesical pressure held constant at 20 cm. H_2O. [A] Upper graphs, stimulation of lateral hypothalamic area with all nerves intact: [B] middle graphs, stimulation of nucleus medialis dorsalis after section of hypogastric nerves; [C] lower graphs, stimulation of nucleus medialis dorsalis after section of hypogastrics bilaterally and pelvics unilaterally

who reported that exclusion of the sympathetic innervation with the sacral nerves intact did not give an appreciable modification of the bladder response. However, the evidence obtained in the present study has shown that division of the hypogastric nerves in an otherwise intact animal altered, occasionally, the contraction of the bladder in one of several ways. In some instances, it shortened, or lengthened, the latent period; in others, it affected the rapidity or even the stability of the contraction. Section of the hypogastrics often diminished and sometimes augmented the contraction; in some experiments, the relaxation that normally follows cessation of stimulation in the sustained contraction was appreciably delayed. In one observation, section of the hypogastrics reversed the type of response from a sustained to an unsustained contraction.

It would seem logical, as Grossman and Wang[24] have suggested, that, since the unsustained contraction elicited from forebrain stimulation so closely resembled that observed after hypogastric nerve excitation, it should be mediated by the sympathetic outflow to the bladder. From the present data, it would appear that the unsustained contraction was more often transmitted to the bladder through the parasympathetic division of the nervous system. Conversely, the hypogastric nerves seemed to play a larger role in the mediation of the sustained contraction, a response usually associated with the activity of the pelvic nerves.

In some of the animals in the present study, in which section of the hypogastrics had no apparent effect, the further insult of sectioning the pelvics on one side abolished the response in all areas of the bladder. This held true for both the excitatory and inhibitory responses. Why the pelvic nerves on one side were not able to support the bladder response was not clear, but a reasonable assumption would be that the hypogastrics did play a role in such reactions.

Other evidence for the participation of the hypogastrics was obtained from section of the pelvic nerves after a reactive point had been established in the forebrain. It was found in some experiments, as Wang and Harrison[15] did, that a small contraction persisted after section of the pelvic nerves. Since this contraction disappeared when the hypogastrics were divided, it was concluded that the sympathetic division does transmit bladder impulses from central sources.

On a number of occasions, a marked relaxation of the bladder wall (generally accompanied by inhibition of the spontaneous rhythm) was observed during stimulation of points in the internal capsule, globus pallidus, entopeduncular nucleus, hypothalamus, optic tract, mammillary body, and several thalamic nuclei. Beattie and Kerr[12] noted such responses when the posterior hypothalamic area was stimulated. Others have elicited inhibitory effects from stimulation of the posterior sigmoid gyrus,[9] anterior hypothalamus,[15] and the septal and preoptic areas together with many diencephalic structures.[23,24] Uvnäs[13] obtained this response only during stimulation of hypothalamic areas at relatively high frequencies, while Gellhorn[10] ascribed inhibition to activity of the adrenomedullary secretion induced by hypothalamic stimulation.

The results presented here are in general agreement with those of others[9,15] who found that the inhibitory response disappeared after section of the parasympathetic outflow to the bladder. In one of the experiments, however, section of the hypogastrics tended to augment the inhibitory effect, while in another animal the reverse was true. The frequency of the stimulating current did not seem to be a significant factor in the inhibitory reaction. It was true that changes in frequency often altered the character of the response, but such data do not justify a classification of frequency rates into any particular pattern of expected responses.

SUMMARY

Bladder responses after stimulation of points within the forebrain were selected from a series of 46 animals for study. General types of responses observed were: [1] sustained contraction, [2] unsustained contraction, [3] relaxation of the detrusor muscle, and [4] relaxation of the detrusor muscle together with inhibition of the spontaneous rhythm of the bladder. Neither the intravesical pressure maintained nor the stimulating frequency employed played any significant role in the

observed response. It was true that changes in frequency often altered the character of the response, but no classification of frequency rates could be fitted into any particular pattern of expected responses.

Section of the hypogastrics altered, occasionally, the bladder response in one of several ways. It shortened or lengthened the latent period or the rapidity or even the stability of the response. Section of the hypogastrics often diminished or augmented the actual amount of contraction or even delayed the relaxation after cessation of stimulation of a forebrain structure. In some few experiments, after section of the pelvic nerves, a small contraction followed by relaxation persisted. From such observations, it has been concluded that, in some instances at least, the hypogastrics played a role in the neural mechanisms of micturition in the cat.

The authors gratefully acknowledge the technical assistance of Mrs. Edith Sully and Mr. John Fields.

REFERENCES

1. Elliott, R. R.: The innervation of the bladder and urethra. J. Physiol. 35:367, 1907.
2. Learmonth, J. R.: A contribution to the neurophysiology of the urinary bladder in man. Brain 54:147, 1931.
3. Langworthy, O. R., Kolb, L. C., and Lewis, L. G.: Physiology of Micturition. Experimental and Clinical Studies with Suggestions as to Diagnosis and Treatment. Baltimore, Williams & Wilkins Co., 1940.
4. MacDonald, A. D., and McCrea, E. D.: Observations on the control of the bladder. The effects of nervous stimulation and of drugs. Quart. J. Exper. Physiol. 20:379, 1930.
5. Kuntz, A., and Saccomanno, G.: Sympathetic innervation of the detrusor muscle. J. Urol. 51:535, 1944.
6. Ingersoll, E. H., Jones, L. L., and Hegre, E. S.: Urinary bladder response to unilateral stimulation of hypogastric nerves. J. Urol. 72:178, 1954.
7. Ingersoll, E. H., and Jones, L. L.: Effect upon the urinary bladder of unilateral stimulation of hypogastric nerves in the dog. Anat. Rec. 130:605, 1958.
8. Girado, J. M., and Campbell, J. B.: The innervation of the urethra of the female cat. Exper. Neurol. 1:44, 1959.
9. Spiegel, E. A., and Hunsicker, W. C., Jr.: The conduction of cortical impulses to the autonomic system. J. Nerv. & Ment. Dis. 83:252, 1936.
10. Gellhorn, E.: Hypothalamus, bladder and gut. A contribution to the understanding of autonomic integration. Acta neuroveg. 19:235, 1958.
11. Lichtenstern, R.: Über die zentrale Blaseninnervation, ein Beitrag zur Physiologie des Zwischenhirns. Wien. klin. Wchnschr. 25:1248, 1912.
12. Beattie, J., and Kerr, A. S.: The effects of diencephalic stimulation on urinary bladder tonus. Brain 59:302, 1936.
13. Uvnas, B.: Effect of frequency of hypothalamic stimulation upon bladder response. Proc. Soc. Exper. Biol. & Med. 64:181, 1947.
14. Ström, G., and Uvnas, B.: Motor responses of gastro-intestinal tract and bladder to topical stimulation of the frontal lobe, basal ganglia and hypothalamus in the cat. Acta physiol. scandinav. 21:90, 1950.
15. Wang, S. C., and Harrison, F.: The nature of bladder responses following stimulation of the anterior hypothalamus. Am. J. Physiol. 125:301, 1939.
16. Hegre, E. S., and Ingersoll, E. H.: An analysis of regional variations in the response of the detrusor muscle to electrical stimulation of the hypogastric nerves. J. Urol. 61:1037, 1949.
17. Jasper, H. H., and Ajmone-Marsan, C.: A Stereotaxic Atlas of the Diencephalon of the Cat. Ottawa, National Research Council of Canada, 1954.
18. Ingersoll, E. H., Jones, L. L., and Hegre, E. S.: Urinary bladder response to unilateral stimulation of pelvic nerves. Proc. Soc. Exper. Biol. & Med. 88:46, 1955.
19. Langworthy, O. R., and Kolb, L. C.: Demonstration of encephalic control of micturition by electrical stimulation. Bull. Johns Hopkins Hosp. 56:37, 1935.
20. Smith, W. K.: Responses from the posterior pyriform cortex. Anat. Rec. 100:713, 1948.
21. Kaada, B. R., Andersen, P., and Jansen, J., Jr.: Stimulation of the amygdaloid nuclear complex in unanesthetized cats. Neurology 4:48, 1954.
22. Shealy, C. N., and Peele, T. L.: Studies on amygdaloid nucleus of cat. J. Neurophysiol. 20:125, 1957.
23. Kabat, H., Magoun, H. W., and Ranson, S. W.: Reaction of the bladder to stimulation of points in the forebrain and mid-brain. J. Comp. Neurol. 63:211, 1936.
24. Grossman, R. G., and Wang, S. C.: Diencephalic mechanism of control of the urinary bladder of the cat. Yale J. Biol. & Med. 28:285, 1955.

Painful ophthalmoplegia

Its relation to indolent inflammation of the cavernous sinus

William E. Hunt, M.D., John N. Meagher, M.D.,
Harry E. LeFever, M.D., and Wolfgang Zeman, M.D.

RETROORBITAL PAIN accompanied by ophthalmoplegia was first described by Charcot, who called it "ophthalmoplegic migraine." This term has been loosely applied to a number of pathologically unrelated disorders that have similar clinical manifestations. Pain and ophthalmoplegia may be caused by [1] aneurysm of the internal carotid artery at the posterior communicating junction, [2] neoplasm, [3] carotid-cavernous fistula, [4] gummatous periostitis about the orbital fissure, or [5] meningovascular syphilis with oculomotor palsy. A dilated sclerotic carotid artery may cause these symptoms by pressure upon the third cranial nerve just prior to its entry into the cavernous sinus (we observed this in a patient with retroorbital pain and oculomotor palsy who was explored in the erroneous belief that the lesion was a saccular aneurysm).

After excluding these identifiable lesions, there remain a number of cases of more obscure etiology. Transitory third cranial nerve palsy probably occurs in some cases of paroxysmal vascular headache of the migraine type. This may be due to dilation and edema of the cerebral arteries adjacent to the oculomotor nerve in the subarachnoid space.[1] The diagnosis of "ophthalmoplegic migraine" should be reserved for these cases.

This paper is intended to define a clinical entity, of somewhat obscure etiology, that cannot be termed "ophthalmoplegic migraine." In the last seven years, we have observed 6 cases of retroorbital pain and involvement of the structures lying within the cavernous sinus and its wall. This syndrome is characterized by the following criteria:

1] Pain may precede the ophthalmoplegia by several days, or may not appear until some time later. It is not a throbbing hemicrania occurring in paroxysms, but a steady pain behind the eye that is often described as "gnawing" or "boring."

2] Neurologic involvement is not confined to the third cranial nerve, but may include the fourth, sixth, and first division of the fifth cranial nerves. Periarterial sympathetic fibers and the optic nerve may be involved.

3] The symptoms last for days or weeks.

4] Spontaneous remission occurs, sometimes with residual neurologic deficit.

5] Attacks recur at intervals of months or years.

6] Exhaustive studies, including angiography and surgical exploration, have produced no evidence of involvement of structures outside the cavernous sinus. There is no systemic reaction.

We believe that the syndrome is caused by an inflammatory lesion of the cavernous sinus. This hypothesis was developed on the basis of the findings and clinical course in our first case. Shortly thereafter, Eduardo Tolosa[2] of the Neurological Institute of Barcelona published the report of a single case that met the above criteria. His patient expired after an exploratory operation, and autopsy showed an inflammatory lesion of the cavernous sinus.

CASE REPORTS

Case 1. V.H., a 31-year-old white female, developed mild diplopia, with no other symptoms, on November 24, 1953. Ophthalmologic

From the Department of Surgery, Division of Neurosurgery, and the Department of Pathology, Ohio State University College of Medicine, Columbus, Ohio.

consultation did not relate the deficit to a specific nerve. A decompensated esotropia or multiple sclerosis was considered the most probable cause. Four weeks later, she awakened with vomiting and severe left retroorbital pain. The strabismus became more marked and definite left third nerve weakness was demonstrated. The pupil did not dilate. Some scintillating scotomata were noted in the left eye.

The patient was admitted to Barnes Hospital, St. Louis, Missouri, under the care of Dr. H. G. Schwartz. Vital signs, peripheral blood count, and urinalysis were normal. Blood urea nitrogen was 15 mg. per cent; blood sugar was 72 mg. per cent. An electroencephalogram was normal. Lumbar puncture released a clear fluid, under normal pressure, containing 3 lymphocytes and 59 mg. per cent of protein. Colloidal gold curve was flat. Consultations with the departments of neurology and otolaryngology were obtained, but no explanation could be found for the disorder. A left carotid arteriogram was normal.

Symptoms disappeared for approximately five days and then returned in a much more severe form. Left retroorbital pain was intense and continuous. The patient clearly differentiated the boring quality of this localized pain from that of her previous rare vascular headaches. These previous headaches had been throbbing, diffusely frontotemporal and right-sided. Pain increased for three weeks, with intermittent vomiting, and then subsided during the next two weeks.

At the peak of the pain, third nerve weakness became more marked, ptosis developed, and fourth and sixth nerve paresis appeared. The left pupil was not dilated, but it reacted sluggishly to light. Some numbness was noted in the first division of the left trigeminal nerve. Scintillating scotomata were pronounced. The fundi remained normal. There was no retinal venous engorgement.

Attempted treatment with intravenous histamine markedly aggravated the pain. Diphenhydramine hydrochloride (Benadryl) may have been of some benefit (50 mg. were given 3 times a day).

Resolution of the extraocular palsies lagged approximately three weeks behind the remission of pain. After complete clinical recovery, there was a third very mild exacerbation of a few days duration. The patient has remained entirely well for the last six and one-half years.

A definite diagnosis was not made at the time. As the syndrome developed, multiple sclerosis, intracranial aneurysm, and invasive malignancy involving the cavernous sinus were considered. With spontaneous remission, it was speculated that the lesion must be an allergic or inflammatory process in the cavernous sinus.

Case 2. S.W., a 57-year-old white female, was admitted to the Ohio State University Hospital on December 27, 1955, complaining of blurred vision, diplopia, and retroorbital pain. Visual disturbances had appeared four weeks before admission; pain had appeared two weeks later. The right eye was completely blind and there was paralysis of all extraocular movements on the right. The pupil was slightly dilated and fixed. On the right side, a mild hypesthesia was present in the supraorbital region and corneal sensitivity was diminished. The involved eye showed some proptosis, but it could be easily displaced back into the orbit. Fundi appeared normal. Ophthalmodynamometer readings showed central retinal artery pressures of 40 mm. on the right and 45 mm. on the left. An electroencephalogram showed mild diffuse slowing over the posterior pole. Roentgenograms of the skull, including orbital views, were not remarkable. Complete blood count, blood urea nitrogen, blood sugar, urinalysis, and cerebrospinal fluid were normal.

On December 29, 1955, right carotid angiography demonstrated a normal vascular tree, including the ophthalmic artery.

On January 4, 1956, the orbital contents were explored through a right frontal craniotomy. The dura was opened and the optic chiasm and basal cisterns were explored. All structures appeared intact and healthy.

The patient's recovery from surgery was rapid and uneventful. On corticosteroid therapy she became pain-free by the fifth postoperative day. Extraocular palsies slowly cleared, but blindness of the involved eye still persists.

Case 3. W.S., a 34-year-old white male Ukrainian laborer, was complaining of severe left supraorbital and retroorbital pain when first seen on April 22, 1956. Two weeks before, he had been exposed to cold at work; that

same night he had developed chills and pain behind the left eye. He awakened the next day with complete ptosis of the left eyelid and partial loss of vision in the left eye.

In 1943, while in a German prison camp, he had been exposed to severe cold. A similar episode of left retroorbital pain, ptosis, and diplopia occurred at that time. Symptoms had disappeared without treatment in approximately six weeks.

He was a healthy young male with normal vital signs; he had no physical or neurologic abnormalities except about the left eye. There was complete paralysis of the muscles supplied by the third cranial nerve and some weakness of the superior oblique muscle. The lateral rectus muscle functioned normally. Visual acuity was 20/20 in the right eye and 20/200 in the left. Some photophobia existed on the left. Peripheral visual fields were not constricted.

Complete blood and spinal fluid studies were normal. Urine tests for porphobilinogen were negative. X-rays of the skull, chest, optic foramina, and superior orbital fissures were not remarkable. An electroencephalogram was normal. A normal left carotid arteriogram was obtained (Fig. 1).

Treatment was begun with 10 mg. of prednisone every six hours for two days; thereafter 10 mg. was given three times daily. Pain promptly diminished. On May 9, 1956, he noted a beginning return of third nerve function and improvement in vision. Pain had disappeared. Visual acuity was 20/20 in the right eye and 20/200 in the left. Visual fields were normal. The left blind spot was 23 x 13 mm.; the right was 7 x 11 mm. Improvement continued, but recovery was still incomplete when he was last seen in November 1959.

These and 3 similar cases (M.D., J.R., and S.T.) are summarized in the table.

Fig. 1. Normal arteriogram in Case 3 (W.S.)

DISCUSSION

We have been reluctant to report these cases because we have no pathologic confirmation of the proposed diagnosis. Nevertheless, aneurysm and neoplastic lesions have been effectively excluded. The remittent nature of the disease has been established by follow-up for periods up to six years.

We attempted to relate this syndrome to previous reports in the literature.

First, we sought references to lesions of the orbital nerves for which no satisfactory etiologic explanation has been provided, such as ophthalmoplegic migraine, syndrome of recurrent ocular palsy, and syndrome of the superior orbital fissure. In commenting on ophthalmoplegic migraine, Wilson[3] stated that "migraine" is probably a misnomer, since the patient usually complains of a gnawing retroorbital pain rather than a throbbing paroxysmal hemicrania. He stated that pain precedes the paralysis. In two of our cases the reverse was true. He cited cases in which tuberculosis, aneurysm neuroblastoma, and fibrochondroma were found at autopsy, but doubted that these should be classed with the group of more benign outcome. He also noted the absence of a strong heredofamilial inci-

SUMMARY OF 6 CASES OF PAINFUL OPHTHALMOPLEGIA

Case	Age at onset	Sex	Number of attacks	Side	Cranial nerves involved	Studies done	Cerebrospinal fluid	Explored	Residual damage
V.H.	31	Female	3	Right	3,4,6,5*,2?	Angiography	Negative	No	None
S.W.	57	Female	1	Right	2,3,4,6,5*	Angiography	Negative	Yes	Yes 4th cranial nerve Blind—right eye
W.S.	20 and 34	Male	2	Left	2,3,4,6	Angiography Pneumoencephalography	Negative	No	None with 1st attack Mild ptosis with 2nd attack
M.D.	53	Female	2	Left	3,4,6 (1st attack) 3 (2nd attack)	Angiography	Negative	No	None
J.R.	9 and 39	Male	2	Right	3 (both attacks) 5* (on 2nd also)	Angiography Biopsy of temporal artery	Negative	No	None
S.T.	15 and 22	Female	2	Right and left	3 (both attacks)	Angiography	Negative	No	None

*First division of the fifth cranial nerve

dence. Verbrugghen[1] thought that in ophthalmoplegic migraine the third cranial nerve is compressed by the adjacent dilated cerebral arteries.

Bramwell[4] discussed a syndrome of recurrent ocular palsy in young people, but proposed no etiology. He mentioned that intracranial aneurysm may cause such symptoms. Haymaker and Kuhlenbeck[5] referred to "spontaneously occurring extraocular palsies," ascribing them to exposure to cold. They cited rheumatic disorders, periorbital periostitis, and vitamin deficiency as possible etiologic processes. They described the acute onset of pain in or about the eye, and involvement of the third, fourth, sixth, and the first division of the fifth cranial nerves. These references indicate that cases similar to ours have been described, but have not been clearly defined clinically or etiologically.

Second, we sought references to ophthalmic complications of recognized inflammatory syndromes.[6–12] Temporal arteritis is a rare condition that seldom appears before age 60; conspicuous inflammation of the superficial temporal arteries occurs in this syndrome. Local signs of tenderness and inflammation usually lead to diagnosis by biopsy. The lesion is nonspecific granulomatous process in the adventitia. The course, while prolonged, is usually benign and self-limited. No mention was made of the tendency to recurrence.

Parsons-Smith[11] reported 15 patients, aged 63 to 80 years, who had this disorder; visual symptoms were various. All showed some systemic reaction. All survived, although visual loss usually persisted. Weakness of the sixth nerve, the superior rectus muscle, and the levator palpebrae superior were mentioned. Allen, Barker, and Hines[6] emphasized that "temporal" arteritis may involve other branches of the carotid. They reported a 40% incidence of ophthalmic disturbances. One instance of third nerve palsy was mentioned, as well as rare deafness and hemiplegia of dubious relationship to the arteritis. Usually blindness was the only sign; it appeared to be caused by retrobulbar involvement of the optic nerve. Recovery of vision did not occur. Otherwise, prognosis was said to be good, and response to cortisone excellent. No relapses were reported.

In periarteritis nodosa, by contrast, there is severe systemic reaction, and the disease terminates fatally in 90% of cases. Blindness, diplopia, seventh or tenth nerve palsies, vertigo, tremor, chorea, fits, hemiplegia, delirium, and coma are described as the disease progresses. The disease is usually seen in young adults.

Mertens, Esslen, and Papst[13,14] described 7 cases of painful ophthalmoplegia that had much in common with our cases—headache, vomiting, and photophobia. The disease tend-

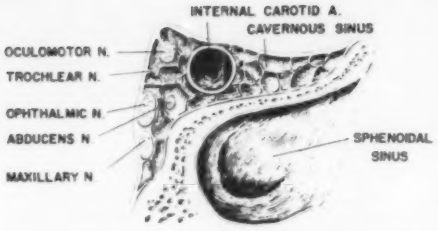


Fig. 2. Coronal section through cavernous sinus. Note proximity of nerves to internal carotid artery.

ed to be remittent and recurrent, and response to corticosteroids was good. Electromyographic examination of the extraocular muscles suggested a local myositis rather than a neurogenic muscle weakness. In 2 cases, an interstitial myositis was demonstrated by biopsy. These cases differed from our series in several important respects, however. The process was usually bilateral, and signs of inflammation within the orbit were common (exophthalmos, edema of the lids, chemosis, and conjunctival injection). The pattern did not follow nerve distribution, and involvement of the trigeminal nerve or the autonomic fibers to the pupil was not mentioned.

On the basis of our clinical observations, we feel justified in postulating the existence of a benign, remittent inflammatory condition within the cavernous sinus and its walls. Pain referral is compatible with this hypothesis. The third, fourth, sixth, and first division of the fifth cranial nerves lie close together in this region (Fig. 2). The optic nerve might well be affected. In the presence of otherwise complete oculomotor palsy, the absence of mydriasis suggests involvement of the pericarotid sympathetic plexus.

The case reported by Tolosa[2] supports this assumption. It concerned a 47-year-old male who presented the signs and symptoms we have described: retroorbital pain, vomiting, paralysis of the third, fourth and sixth cranial nerves, and a diminished corneal reflex. He had experienced a similar episode three years before, with spontaneous recovery. Angiography showed a suggestive narrowing of the carotid siphon just distal to the cavernous sinus. Death occurred on the third day after a negative intracranial exploration. At autopsy, to quote Dr. Tolosa, "the intracavernous portion of the carotid artery was wrapped in granulomatous tissue which did not obstruct the lumen of the sinus." The process invested the adjacent cranial nerves. Dr. Tolosa's slides were made available to us and have been reviewed.

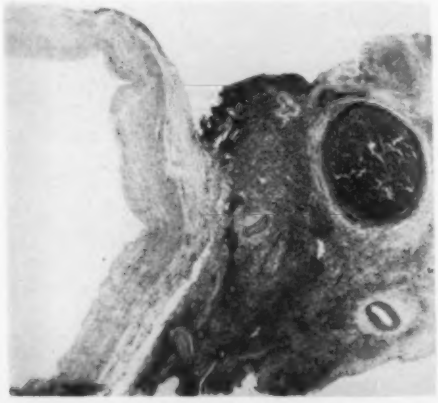


Fig. 3. The carotid artery is fused to the abducens nerve by a granulomatous lesion. Hematoxylin-eosin; 20:1. (Slide by courtesy of Dr. Tolosa)

The region where the carotid artery enters the cranial cavity by penetrating the outer wall of the cavernous sinus is the site of a low-grade, nonspecific inflammatory process (Fig. 3). This process is characterized by a proliferation of fibroblasts and by infiltration of the septa and wall of the sinus with lymphocytes and plasma cells (Fig. 4). There is no necrosis and no polymorphonuclear cells are present. No fibrinoid collagen degeneration is observed. The adventitia of the carotid artery, as well as of the smaller vessels, is only incidentally infiltrated by the chronic inflammatory cells.

There is no evidence that the process is primarily an arteritis. The granulomatous lesion has engulfed the abducens nerve and all small connecting branches of the carotid plexus and the ophthalmic division. Myelin sheaths are fully preserved and no inflammatory changes are seen within the perineurium (Fig. 5). The dense collagenous layers of the dura

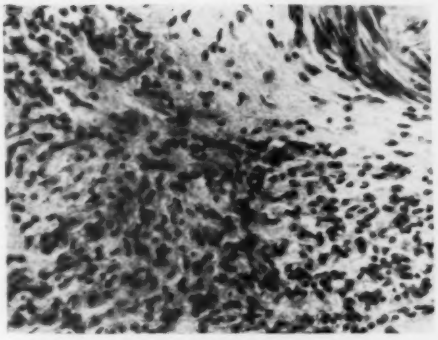


Fig. 4. Granulomatous tissue. Note the scarcity of vessels and infiltration by lymphocytes and plasma cells. Hematoxylin-eosin; 400:1. (Slide by courtesy of Dr. Tolosa)

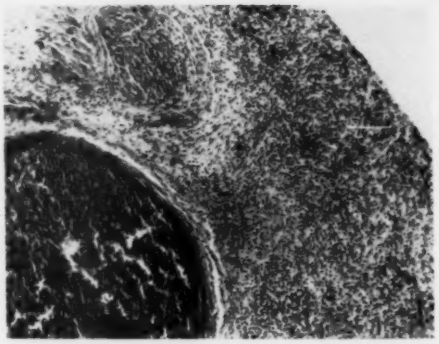


Fig. 5. Motor (below) and sensory (above) branches of abducens nerve surrounded by granulomatous tissue. The perineurium is thickened, the myelin sheaths are well-preserved. Hematoxylin-eosin; 80:1. (Slide by courtesy of Dr. Tolosa)

are loosened by inflammatory exudates and edema (Fig. 6). It is easily understood that such inflammatory changes, in a tight connective tissue, may exert pressure upon the penetrating nerves. The etiology of this process is obscure. Its pathogenesis could conceivably be explained by an infection of the sphenoidal sinus, but this assumption must await verification.

This case meets all criteria for the syndrome we have described, including remission after the first attack. Our cases lack only autopsy confirmation.

We feel justified in proposing the diagnosis of intracavernous carotid periarteritis for the following reasons: [1] the lesion is unquestionably within the cavernous sinus, [2] it is remittent, and [3] other causes have been excluded by angiography and exploration. It cannot be identified with temporal arteritis or periarteritis nodosa because of its localized involvement, absence of systemic reaction, and benign course.

On the basis of informal reports from other neurologists and neurosurgeons, it seems that the condition does occur sporadically. No description of it exists in American literature, and the surgeon who encounters an isolated case of focal progressive neurologic deficit is tempted to explore the involved region. This is dangerous and unnecessary. In severe cases, complete relaxation of the ocular muscle cone permits proptosis. This must not be taken as evidence of a mass lesion. Absence of a palpable orbital mass, absence of retinal venous engorgement, and the ease with which the globe can be pushed back into the orbit are sufficient evidence to exclude orbital tumor. Angiography is an essential adjunct in ruling out aneurysm or mass lesion.

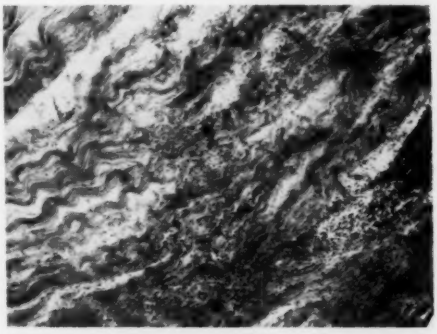


Fig. 6. Lateral wall of cavernous sinus (dura mater) with focal accumulations of chronic inflammatory cells and edema. Hematoxylin-eosin; 80:1. (Slide by courtesy of Dr. Tolosa)

The nature of the postulated lesion suggests treatment with corticosteroids; such treatment was used for 5 of our 6 cases. While spontaneous remissions are known to occur, prompt

improvement followed corticosteroid therapy in all 5 cases.

SUMMARY

1. A syndrome of recurrent unilateral retro-orbital pain with extraocular palsies and occasional blindness is described.

2. This syndrome is believed to be caused by a low-grade, nonspecific inflammation of the cavernous sinus.

3. Careful history and physical examination, supported by negative angiography, are sufficient for making the diagnosis. Surgical exploration is unnecessary.

4. Although spontaneous remission occurs, corticosteroid therapy probably is of value.

REFERENCES

1. Verbrugghen, A.: Pathogenesis of ophthalmoplegic migraine. Neurology 5:311, 1955.
2. Tolosa, E.: Periarteritic lesions of carotid siphon with clinical features of carotid infraclinoidal aneurysm. J. Neurol. Neurosurg. & Psychiat. 17:300, 1954.
3. Wilson, S. A. K., and Bruce, N.: Neurology, ed. 2. Baltimore, Williams & Wilkins, 1940, vol. 2. pp. 1298-99 and 1580-81.
4. Bramwell, E.: Upon (1) leaking aneurysms of the cerebral arteries as a cause of third nerve paralysis, with special reference to two cases in which the diagnosis was confirmed by arterial radiography; (2) a note upon the aetiology of recurrent and periodic ocular palsy and ophthalmoplegic migraine. Tr. Ophth. Soc. U. Kingdom 54:205, 1934.
5. Haymaker, W., and Kuhlenbeck, H.: Diseases of the brainstem and its cranial nerves. In Baker, A. B.: Clinical Neurology, New York, Harper & Bros., 1955, vol. 2. p. 1260.
6. Allen, E. V., Barker, N. W., and Hines, E. A.: Peripheral Vascular Diseases. Philadelphia, W. B. Saunders Co., 1946. pp. 479-482.
7. Davenport, R. C., Meadows, S. P., and Duguid, J. B.: Discussion: inflammatory vascular diseases affecting eyes Tr. Ophth. Soc. U. Kingdom 74:5, 1954.
8. Glaser, G. H.: Neurologic manifestations in collagen diseases; problems of prognosis and treatment. Neurology 5:751, 1955.
9. Kernohan, J. W., and Woltman, H. W.: Periarteritis nodosa. Proc. Staff Meet., Mayo Clin. 12:554, 1937.
10. Mackay, M. E., McLardy, T., and Harris, C.: Case of periarteritis nodosa of central nervous system. J. Ment. Sc. 96:470, 1950.
11. Parsons-Smith, G.: Ophthalmic manifestations of temporal arteritis. Brit. J. Ophth. 36:615, 1952.
12. Summers, V. K.: Nervous manifestations of periarteritis nodosa. Lancet 1:1148, 1950.
13. Mertens, H. G., Esslen, E., and Pabst, W.: Die oculären Myopathien. II. Mitteilung. Die chronische oculäre Myositis. Nervenarzt 29:120, 1958.
14. Mertens, H. G., Esslen, E., and Pabst, W.: Die oculären Myopathien. III. Mitteilung. Die oligosymptomatische oculäre Myositis. ("Pseudomyasthenie"). Nervenarzt 29:213, 1958.

Cerebrovascular disease

VI. Relationship to disease of the heart and the aorta

A. B. Baker, M.D., A. Iannone, M.D., and J. Kinnard, M.D.

WITHIN RECENT YEARS, there has been increasing interest in the possible relationship of atherosclerotic changes in the brain to similar alterations in the heart and the aorta. This interest has centered upon [1] the developmental sequence of the atherosclerotic changes in the brain, coronary arteries, and aorta[1–5] and [2] the actual influence of cardiac disease upon cerebral atherosclerosis.[6–9] Because of the importance of such studies, it was felt that further extension of prior observations on a carefully surveyed autopsy series might prove of value. The advantage of the present study was that the degenerative changes in the various organ systems were studied and coded in consecutive autopsy cases by the same investigator (A.B.B.). This allowed for greater uniformity of findings and less margin of error which invariably results when different investigators attempt to use even the same coding system.

METHOD OF STUDY

For the past three years, preliminary studies have been carried out on the atherosclerotic changes of the cerebral arteries, coronary arteries, and aorta in an attempt to work out a simple gross coding system for the severity of such changes. It was apparent at the onset that a different coding system would have to be used for each of these vessel groups, since the nature of the degenerative process in each seemed to differ considerably on gross examination. The following coding systems were finally adopted (coding guide):[10]

Arteries of the circle of Willis

1+: Opacity to a very thin plaque that involves only a small part of the vessel circumference but causes no lumen narrowing

2+: [A] A thin plaque that involves over half the vessel circumference with minimal lumen narrowing. [B] A small, thick plaque that produces less than 25% lumen narrowing

3+: [A] A thin plaque that involves the entire circumference of the vessel with mild lumen narrowing. [B] a localized plaque that produces from 25 to 50% lumen narrowing

4+: [A] A thick plaque that involves the entire vessel circumference with moderate or marked lumen narrowing (pipestem). [B] A localized plaque resulting in over 50% lumen narrowing.

By means of the above coding system, the severity of the degenerative changes were recorded at 28 different areas in the circle of Willis (Table 1). Each of these areas was graded from 0 to 4+ atherosclerosis. The total numerical value for the degree of atherosclerosis present in a single case was then obtained by multiplying each of the 28 areas by the severity of the atherosclerosis present in each area and adding the total. Thus, since there were 28 areas measured and the greatest degree of atherosclerosis was 4+, the greatest severity of atherosclerosis possible in any single case was 28 x 4, or 112. Actually, none of the cases showed such severe changes since many of the vessels studied were only minimally involved, even in the presence of generally intense changes. The majority of even the most severely implicated cases rarely exceeded 30 to 50 points of total change. Once the total points of atherosclerosis were determined, the cases were arbitrarily divided into 4 groups: [1] no atherosclerosis; [2] mild changes (1-10 points of atherosclerosis);

From the Division of Neurology, University of Minnesota Medical School, Minneapolis.

TABLE 1
AREAS OF CIRCLE OF WILLIS CODED FOR ATHEROSCLEROSIS

1.	Anterior communicating
2.	Upper basilar
3.	Middle basilar
4.	Lower basilar
5.	Right anterior cerebral proximal to the anterior communicating
6.	Left anterior cerebral proximal to the anterior communicating
7.	Right anterior cerebral distal to the anterior communicating
8.	Left anterior cerebral distal to the anterior communicating
9.	Right internal carotid up to the trifurcation
10.	Left internal carotid up to the trifurcation
11.	Right internal carotid at the trifurcation
12.	Left internal carotid at the trifurcation
13.	Right middle cerebral (first third)
14.	Left middle cerebral (first third)
15.	Right middle cerebral at or beyond first branch
16.	Left middle cerebral at or beyond first branch
17.	Right posterior communicating
18.	Left posterior communicating
19.	Right posterior cerebral (first third)
20.	Left posterior cerebral (first third)
21.	Right posterior cerebral beyond first third
22.	Left posterior cerebral beyond first third
23.	Right superior cerebellar
24.	Left superior cerebellar
25.	Right vertebral
26.	Left vertebral
27.	Right posterior inferior cerebellar
28.	Left posterior inferior cerebellar

[3] moderate changes (11-20 points of atherosclerosis); and [4] severe changes (over 21 points of atherosclerosis).

Coronary arteries. Each of the 3 main arteries of the heart was coded separately after opening of the vessel and examination of the entire extent of the descending, circumflex, and right branches.

1+: A few scattered plaques covering less than 25% of the vessel lumen but with lumen narrowing of less than 25%

2+: Many plaques covering over 25% of vessel wall but with lumen narrowing of less than 25%

3+: Same as 2+ but with lumen narrowing from 25 to 50% and often with some calcification

4+: Same as 3+ but with extensive calcification and lumen narrowing of over 50%.

Aorta. The entire vessel was opened and the changes recorded for the entire extent of the vessel.

1+: Occasional plaques involving less than 25% of the vessel wall, with or without occasional small thrombi

2+: Many diffuse plaques covering over 25% of vessel wall but with no lumen narrowing

3+: Same as 2+ but with occasional calcification, ulceration, or thrombi

4+: Many diffuse, almost continuous plaques with extensive calcification, ulceration, and thrombi and definite lumen narrowing.

Using the above coding systems, one of the authors (A.B.B.) personally studied 485 consecutive autopsies at the Ulleval Hospital in Oslo, Norway, and recorded the degree of atherosclerosis in each of the 3 groups of vessels in each of these cases.

RELATIONSHIP OF CEREBRAL ATHEROSCLEROSIS TO SIMILAR CHANGES IN HEART AND AORTA

As early as 1906, Brooks[11] reported a comparative study of 367 cases in which he observed the most frequent changes in the coronary vessels, with 270 of 308 cases involved by this process. In the cerebral vessels of the same cases, only 132 were implicated. Unfortunately, no attempt was made to correlate these changes with age and no real quantitative coding system was used. In 1951, Duff and McMillan[12] stated that atherosclerosis affects the cerebral arteries much later in life than the coronary arteries; however, no data was offered to substantiate such a statement.

The first detailed report using a well documented coding system was published in 1957 by Gore and Tejada.[13] These investigators studied primarily the degenerative changes in the aorta and compared these changes with those occurring in the heart and brain. No attempt was made to carry out a comprehensive study of the cerebral vessels. They concluded that atherosclerosis occurs earliest in the aorta and that there is a consistent lag in the development of this process in the coronary and cerebral vessels.

In 1958, Winter and his associates[5] studied 239 cases in which careful observations were made of the atherosclerotic changes in the cerebral vessels. These alterations were then compared with the degenerative changes found in the coronary vessels of the same cases by another group of investigators and reported at a previous time. They found that coronary atherosclerosis was more severe than

cerebral atherosclerosis in the same decade and that the cerebral changes did not approximate those in the coronary arteries until the ninth decade of life. They found that, in any single case, the degree of atherosclerosis in the cerebral arteries may vary widely from that in the coronary arteries.

Moossey[1] in 1958 reported a comparative study of the initial atherosclerotic changes of the aorta and the coronary and cerebral vessels in 122 cases. These changes were determined by the presence of fatty streaks as demonstrated by the Sudan stain. He felt that the earliest changes appeared first in the aorta during the first decade of life and last in the brain during the third decade.

Roberts, Moses, and Wilkins[2–4] studied the degenerative changes in vessels in various areas of the body in 347 selected cases using a standardized coding system. They found the most severe changes in the abdominal aorta in all decades. Cerebral atherosclerosis started later and remained less severe than that in the visceral vessels of the same size.

Our studies consisted of a consecutive series of 485 cases studied in Oslo, Norway, in which the degenerative changes in the brain, coronaries, and aorta were studied grossly by the method described. It is to be pointed out that this study has 2 defects. First, the number of younger patients was limited to only 15 individuals under the age of 35 years. This makes a careful analysis of findings in this younger age group impossible. Secondly, since our study was a gross one, any lesions that could not be seen with the naked eye would have been overlooked. This makes it entirely possible that some of the earliest lesions were not tabulated and may well alter our findings in regard to the exact time of onset of this degenerative process. However, our findings are of significance in that they allow for an excellent picture of the progress of the more advanced lesions and of the total picture of the degenerative process. It is to be emphasized that we were not concerned with the isolated plaque but with the total extent and severity of this process in the various vessel groups.

Table 2 contains our findings as to the atherosclerotic process in the aorta and the coronary and cerebral vessels. We have deliberately initiated our tabulations at age 35, at which period sufficient cases were available to offer significant observations. According to our criteria, it is readily apparent that our findings for the earliest alterations roughly agree with those already published by many investigators. Apparently, in each decade, the aorta is most frequently implicated, followed next by the coronary arteries and finally by the cerebral vessels (Table 2).

The most interesting observation in this respect, however, is noted in the total severity of

TABLE 2
COMPARISON OF DEGREE OF INVOLVEMENT OF BRAIN ARTERIES, CORONARIES AND AORTA

		None				
	Brain		Coronaries		Aorta	
Age	Number	Per cent	Number	Per cent	Number	Per cent
36-45	19:22	86.0	8:17	47.0	8:17	47.0
46-55	26:51	51.0	16:42	38.0	13:40	33.0
56-65	39:125	31.0	18:88	20.0	9:97	9.3
66-75	22:163	13.4	12:127	9.4	4:134	3.0
76-85	7:147	5.0	4:116	3.4	6:129	4.6
86 —	4:35	11.4	1:28	3.6	0:33	0.0
		Severe				
36-45	0:22	0.0	1:17	6.0	0:17	0.0
46-55	6:51	12.0	5:37	13.5	3:47	6.0
56-65	46:125	37.0	21:88	24.0	19:97	20.0
66-75	88:163	51.0	44:127	35.0	34:134	25.0
76-85	103:147	70.0	39:116	34.0	46:129	36.0
86 —	27:35	77.0	13:34	38.0	14:33	42.0

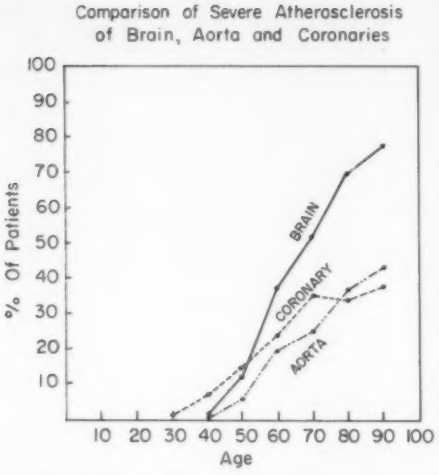


Fig. 1. Comparison of severe atherosclerosis of the brain, aorta, and coronary arteries. Note that, beyond the fifth decade, the cerebral vessels show the most severe involvement.

atherosclerotic changes in these 3 vessel groups when compared by decades. Here the picture changes radically. It is apparent (Table 2) that, for most age groups, although the aorta is the earliest involved by the atherosclerotic process, it is the least severely implicated. The cerebral vessels beyond the fifth decade are much more often severely involved by the atherosclerotic process than either of the other 2 vessel groups (Fig. 1).

Our observations must suggest some caution in concluding that, because a vessel is most readily and most frequently implicated by the atherosclerotic process, it will also be most severely damaged. Apparently, the atherosclerotic process, once initiated, does not necessarily proceed at a uniform rate in all vessels. It is important, therefore, in a study of this process not only to investigate the factors that initiate this process but also to study the possible factors that influence the rate of progress of this important disease process.

When one considers the total population, it is apparent that, although the atherosclerotic process proceeds at different rates in the different organ systems, there is some uniformity in the systems involved, with the earliest changes appearing in the aorta and the most severe changes in the brain. When one considers individual cases, however, much less uniformity of involvement is observed. Some individuals may have severe changes in one organ system with little or no involvement in the others (Table 3). This observation must be kept in mind since it strongly emphasizes the need to exert great caution in arriving at conclusions regarding the extent of the nature of the atherosclerotic process in any single organ system on the basis of clinical implication of other arteries in a single case. This lack of correlation of atherosclerosis in the individual case is also brought out when one compares the frequency of cerebrovascular deaths with the severity of coronary alteration as seen at autopsy (Table 4). As many as 13 of our 57 cases of cerebrovascular deaths (23%) occurred in patients with a minimal degree of coronary atherosclerosis. On the other hand, only 7 or 12% of our cerebrovascular deaths occurred in patients with severity of 4+ coronary disease.

TABLE 3
CEREBRAL ATHEROSCLEROSIS AS COMPARED TO CHANGES IN THE CORONARY VESSELS

Degree of changes in coronary arteries	*Degree of atherosclerosis of large cerebral vessels*			
	None	*Mild*	*Moderate*	*Severe*
None	34 or 60%	15 or 28%	3 or 6%	3 or 6%
1+	29 or 29%	40 or 40%	13 or 13%	18 or 18%
2+	18 or 13%	32 or 23%	30 or 21%	60 or 43%
3+	4 or 7%	9 or 17%	15 or 28%	26 or 48%
4+	3 or 5%	18 or 30%	12 or 20%	27 or 45%

TABLE 4
CEREBROVASCULAR ACCIDENT DEATHS—RELATED TO DEGREE OF CORONARY DISEASE

Age	*Number*	*0*	*1+*	*2+*	*3+*	*4+*	*Total*
46-50							
51-55	1			1			1
56-60							
61-65	5		1	2		2	5
66-70	9		5	4			9
71-75	11		1	4	4	2	11
76-80	12		3	8	1	1	13
81-85	16		3	8	4	2	17
91 —	1				1		1
Total	55		13	27	10	7	57

EFFECT OF HIGH BLOOD PRESSURE ON CEREBRAL ATHEROSCLEROSIS

For many years, it has been a commonly accepted medical concept that there is a definite sequential relationship between the atherosclerotic process and hypertension.[14,15] Many investigators have felt that this heightened intravascular tension results in a mechanical stress exerted on the vascular wall, chiefly at the sites of vascular fixation or bifurcation, and that this mechanical trauma plays an important role in the intimal changes which comprise the atherosclerotic process. It is well known that hypertension does play a very important role in accentuating the arteriolar changes throughout the body, including the brain.[16,17] Baker and Iannone[18] have shown that the medial fibrosis of the intracerebral arterioles is definitely accentuated by the hypertensive process. However, it still is not definite whether hypertension has a similar effect upon the intimal alterations which characterize the atherosclerotic process in the larger basilar vessels. Certainly, some of the more recent studies have suggested that this might well be true. Winters and his associates[5] made a comparative study of a few vessels of the circle of Willis in 239 cases in individuals with and without hypertension, using the heart weight as an index of hypertension. They found that there was the same amount of atherosclerosis up to the fourth decade. After the fourth decade, the hypertensive persons showed more severe changes than did the normotensive persons. Wilkins, Roberts, and Moses,[4] also using heart weight as an index of hypertension, reported on 500 cases. In males, the hypertensive subjects showed a greater degree of both coronary and cerebral

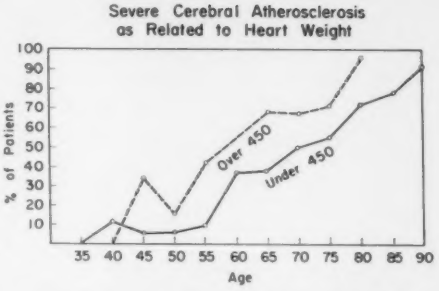


Fig. 2. Severe atherosclerosis as related to heart weight. In all decades, patients with heavier hearts showed more intense cerebral atherosclerosis.

atherosclerosis. The incidence was even more marked in females, particularly those who were obese.

In our studies, we also selected to use heart weight as the best criterion for the presence of hypertension. We selected an arbitrary figure of 450 gm. as our index of hypertension. It is apparent from Table 5 that hypertension as indicated by heart weight appears to play a definite role in cerebral atherosclerosis. In all decades, the frequency and intensity of cerebral changes were greater in individuals with heart weights over 450 gm. As seen in Figure 2, the difference in severe cerebral atherosclerosis in these 2 groups was as high as 30% in the sixth decade. These observations are in agreement with those of Winter and his associates.[5]

It was felt that it might be of value to use the heart weight as a base line and to determine the possibility of severe cerebral changes in individuals who have normal or enlarged

TABLE 5
RELATION OF HEART WEIGHT TO SEVERE ATHEROSCLEROSIS

Age	*Severe atherosclerosis*	*Heart weight over 450 gm.*	*Per cent*	*Severe atherosclerosis*	*Heart weight under 450 gm.*	*Per cent*
36-45	0	5	0%	1	17	6%
46-55	4	19	21%	2	32	6%
56-65	27	53	51%	17	72	24%
66-75	43	63	68%	43	96	45%
76-85	37	45	82%	59	94	63%
86 —	1	4	?	25	30	83%

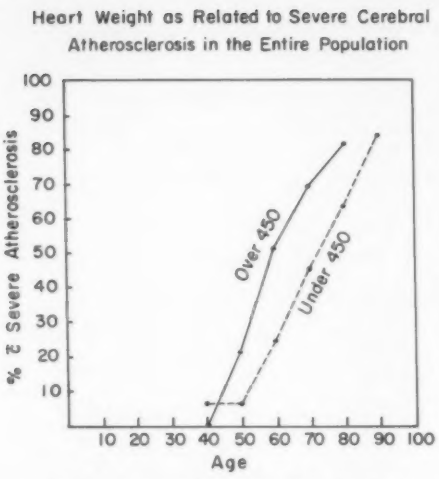


Fig. 3. Heart weight as related to the possibility of severe cerebral atherosclerosis. It is apparent that individuals with heavy hearts have a much greater chance of having severe cerebrovascular changes.

hearts (Fig. 3). As can be seen, individuals in the sixth decade of life with enlarged hearts have a 50% chance of severe cerebral changes as compared to a figure of 24% for those with normal-sized hearts. Such observations may well prove of clinical value.

In our studies on the relationship of cerebral atherosclerosis to cardiac changes, we have had an opportunity to make certain observations on coronary artery disease independent of its relationship to the brain. It is felt that a discussion of these observations might properly supplement this report on brain-heart interrelationship. It is a widely held opinion that during the past fifty years there has been a marked increase in coronary heart disease. Indeed, according to the National Office of Vital Statistics,[19] the recorded death rate from heart disease in the United States has risen from 9% in 1900 to 40% in 1956. Wood[20] has indicated that, in England alone, the number of patients dying from coronary disease per million persons living has increased from 48 in 1926 to 1,392 in 1953. As early as 1932, Bolduan and Bolduan[21] questioned this "appalling increase." Mann[22] suggested that this rise in coronary heart disease was more apparent than real. He felt that much of this increase may be due to unreliability of death certification. He cited 2 studies showing a disparity of as high as 33% between the clinical diagnosis and the actual autopsy verification of coronary death. Lew[23] concluded from his study that 30% of the increase in the crude death rate from coronary heart disease from 1940 to 1955 was due to increasing age of the population, that 40% was due to changes in methods of death certification, and that the major part of the remaining 30% was due to a broader concept, increasing usage, and better diagnosis of coronary heart disease. He concluded that probably less than 15% represents a real increase in coronary heart disease.

It becomes clear that any definite conclusion drawn regarding actual, coronary heart disease must be backed by pathologic observations. To do this, it is immediately apparent that even pathologically a definition of terms is necessary, since pathologically 3 definite entities play a role in the term coronary heart disease—coronary atherosclerosis, coronary thrombosis, and coronary insufficiency as a result of fibrosis. It is entirely possible that the fundamental etiologic factors in each may be different. It is with the hope of casting some light on the above that we have analyzed our cases, in all of which a single individual carried out the complete studies on the heart. We have had the opportunity to compare 2 of the above factors—actual coronary atherosclerosis as classified by our coding system and coronary thrombosis resulting in myocardial changes, as obserevd at autopsy. A study of these 2 factors is presented in Table 6. As can be seen, in the individual case, there is a distinct difference in these 2 factors. Patients may have a minimal degree of coronary atherosclerosis and still have thrombosis adequate to cause death; 3 of our patients had only a single small atherosclerotic plaque on the coronary arteries and still had complete coronary occlusion and death presumably as a result of thrombosis. This observation is in accord with the findings of Yater and his associates.[24] These investigators found, in series of 950 autopsied cases of men dying of coronary heart disease, that thrombotic occlusion alone was the important factor in the death of

men under the age of 40 years. It would appear from our studies that coronary thrombosis may be the predominating pathology of myocardial infarction in any age in individuals in whom little or minimal atherosclerosis of the coronary vessels exists. Indeed, Duguid[25,26] suggests that narrowing of the coronary lumen is due initially to intravascular clotting, which may eventually cause atheromatous changes.

It is also interesting to note that 70 of our patients had very severe atherosclerosis but only 37% of these had clinical coronary disease. In a number of these patients, the coronary arteries were almost completely closed and still there was no evidence of clinical insufficiency. This supports Lober's[27] observation that severe coronary disease must exist before giving rise to clinical symptoms. He concluded that there must be a large reserve capacity in the coronary circulation. Eros, Beyer, and Holmes[28] made similar observations in 300 autopsies performed on battle casualties with no known clinical evidence of coronary heart disease. In this group, 77.3% of the hearts showed some gross evidence of coronary disease, ranging from fibrous thickening to complete occlusion of one or more of the major vessels. Such observations emphasize the fact that any conclusions drawn about the frequency or intensity of coronary artery disease must be based on autopsy studies. Clinical correlations alone not only would miss many severe cases of coronary atherosclerosis but would include mild cases in which a superimposed thrombus results in dramatic clinical symptoms and findings.

TABLE 6
RELATIONSHIP OF CORONARY ATHEROSCLEROSIS TO MYOCARDIAL INFARCTION

	No atherosclerosis		1+ atherosclerosis		2+ atherosclerosis		3+ atherosclerosis		4+ atherosclerosis		
Age	Number of patients	Number of infarctions	Number of patients	Number of infarctions	Number of patients	Number of infarctions	Number of patients	Number of infarctions	Number of patients	Number of infarctions	Total infarctions
31–35	0	0	2	0	2	0	0	0	0	0	0
36–40	2	0	3	0	0	0	0	0	0	0	0
41–45	5	0	2	0	3	0	1	0	0	0	0
46–50	9	0	5	0	3	0	0	0	1	0	0
51–55	4	0	6	1	3	0	3	0	2	2	3
56–60	13	0	15	0	11	4	4	2	0	0	6
61–65	4	0	10	0	13	5	4	1	13	6	12
66–70	8	0	19	1	15	2	6	1	9	5	9
71–75	3	0	18	0	19	4	18	1	11	5	10
76–80	4	0	11	0	31	1	5	1	12	3	5
81–85	0	0	9	1	20	0	6	0	16	5	6
86–90	1	0	1	0	7	0	5	0	5	0	0
91 —	0	0	1	0	5	0	2	0	1	0	0
Total	53	0	102	3	132	16	54	6	70	26	51

CONCLUSIONS

A comparative study of atherosclerosis of the coronary arteries, aorta, and cerebral arteries was carried out in 485 consecutive autopsy cases. A standard coding system was developed to grade the degree of involvement in each of these vessel groups, and the same investigator carried out all the studies in each case.

Atherosclerotic changes occurred most frequently in the aorta, followed by the coronary and finally the cerebral arteries. By the sixth decade of life, only 9% of the cases failed to show changes in the aorta as compared to

20% for the coronary arteries and 31% for the cerebral vessels.

In contrast to this frequency of involvement, the aorta showed the least amount of severe changes. On the other hand, the cerebral vessels, which were the least frequently involved, showed the most severe changes. This would suggest that atherosclerosis, once initiated, does not necessarily proceed at a uniform rate in all vessels and that a study of this process must include not only the possible etiologic factors but also those that tend to accentuate this process.

Although the atherosclerotic process appeared to proceed at different rates in the different organ systems, this did not hold true for the individual case, where there was often little correlation between the frequency and intensity of the atherosclerotic process in the different vessels. Such observations suggest caution in trying to predict the degree of atherosclerosis in one organ system from clinical or pathologic observations on another system.

Generally, individuals with heart weights of over 450 gm. showed more frequent and severe atherosclerotic changes in the cerebral vessels in all age groups.

Apparently, there was no accurate correlation between coronary atherosclerosis and death due to coronary thrombosis with myocardial infarction; 3 patients with only a single small plaque of coronary atherosclerosis died of coronary thrombosis, while 63% of the patients with severe coronary atherosclerosis had no clinical or pathologic evidence of coronary insufficiency. These findings would strongly indicate that any conclusions as to the incidence of coronary heart disease must be based on studies which differentiate between coronary atherosclerosis and coronary thrombosis and therefore must be determined by pathologic observations.

REFERENCES

1. Moossy, J.: Development of cerebral atherosclerosis in various groups. Neurology 9:569, 1959.
2. Roberts, J. C., Moses, C., and Wilkins, R. H.: Autopsy studies in atherosclerosis. Circulation 20: 511, 1959.
3. Roberts, J. C., Wilkins, R. H., and Moses, C.: Autopsy studies in atherosclerosis. II. Distribution and severity of atherosclerosis in patients dying with morphologic evidence of atherosclerotic catastrophe. Circulation 20:520, 1959.
4. Wilkins, R. H., Roberts, J. C., and Moses, C.: Autopsy studies in atherosclerosis. III. Distribution and severity of atherosclerosis in the presence of obesity, hypertension, nephrosclerosis, and rheumatic heart disease. Circulation 20:527, 1959.
5. Winter, M. D., Sayre, G. P., Millikan, C. H., and Barker, N. W.: Relationship of atherosclerosis of the internal carotid system in the brain of women to age and coronary atherosclerosis. Circulation 18:7, 1958.
6. Creed, D. L., Baird, W. F., and Fisher, E. R.: Severity of aortic arteriosclerosis in certain diseases. Am. J. M. Sc. 230:385, 1955.
7. White, N. K., Edwards, J. E., and Dry, T. J.: Relationship of degree of coronary atherosclerosis with age, in men. Circulation 1:645, 1950.
8. Gore, I., and Hirst, A. E., Jr.: Comparative severity of atherosclerosis in the aorta, coronary arteries and cerebral arteries. Am. J. Path. 33:595, 1957.
9. Master, A. M.: Hypertension and coronary occlusion. Circulation 8:170, 1953.
10. World Federation of Neurology: Collaborative Study of Epidemiologic Factors in Cerebrovascular Disease, Coding Guide. Antwerp, 1959.
11. Brooks, H.: Preliminary study of visceral arteriosclerosis. Am. J. M. Sc. 131:778, 1906.
12. Duff, G. L., and McMillan, G. C.: Pathology of atherosclerosis. Am. J. Med. 11:92, 1951.
13. Gore, I., and Tejada, C.: Quantitative appraisal of atherosclerosis. Am. J. Path. 33:875, 1957.
14. Moschcowitz, E.: Cause of arteriosclerosis. Am. J. M. Sc. 178:244, 1929.
15. Beneke: Über die Anfänge der Arteriosklerose. Klin. Wchnschr. 9:2182, 1930.
16. Fishberg, A. M.: Anatomic findings in essential hypertension. Arch. Int. Med. 35:650, 1925.
17. Gull, W. W., and Sutton, H. G.: On pathology of morbid state commonly called Bright's disease with contracted kidney. Med. Chir. Trans. 55:273, 1872.
18. Baker, A. B., and Iannone, A.: Cerebrovascular disease. III. The intracerebral arterioles. Neurology 9:441, 1959.
19. U.S. Dept. of Health, Education and Welfare, National Office of Vital Statistics: Estimated numbers of deaths and death rate for selected causes. Monthly Vital Statistics Rep. 5:10, 1956.
20. Wood, P. H.: Diseases of the Heart and Circulation. 2d ed. Philadelphia, Lippincott, 1956.
21. Bolduan, C. F., and Bolduan, N. W.: Is the "appalling increase" in heart disease real? J. Prevent. Med. 6:321, 1932.
22. Mann, G. V.: The epidemiology of coronary heart disease. Am. J. Med. 23:463, 1957.
23. Lew, E. A.: Some implications of mortality statistics relating to coronary artery disease. J. Chronic Dis. 6:192, 1957.
24. Yater, W. M., Welsh, P. P., Stapleton, J. F., and Clark, M. L.: Comparison of clinical and pathologic aspects of coronary artery disease in men of various age groups. Ann. Int. Med. 34:352, 1951.
25. Duguid, J. B.: Thrombosis as a factor in the pathogenesis of coronary atherosclerosis. J. Path. & Bact. 58:207, 1946.
26. Duguid, J. B., and Robertson, W. B.: Effects of atherosclerosis on the coronary circulation. Lancet 1:525, 1955.
27. Lober, P. H.: Pathogenesis of coronary sclerosis. Arch. Path. 55:357, 1953.
28. Eros, W. F., Beyer, J. C., and Holmes, R. H.: Pathogenesis of coronary disease in American soldiers killed in Korea. J.A.M.A. 158:912, 1955.

Localization of adenosinetriphosphatase in capillaries of the brain as revealed by electron microscopy

Richard M. Torack, M.D.,* Martin Besen, B.S., and Norwin H. Becker, M.D.

In recent studies of cerebral fluid imbalance,[1,2] swelling and loosening of endothelial cells was a constant morphologic change. This cellular alteration did not correlate with the presence or absence of a blood-brain barrier, the preservation of which was determined by the use of colloidal dyes. Therefore, it was logical to believe that a functional mechanism, which could not be visualized by routine technics, may be involved in the regulation of capillary permeability in the brain.

The development of enzyme histochemistry in recent years has enabled investigators to study more adequately the function of normal and altered cells. Some of these technics utilize heavy metals in the capture of the reaction product. Since heavy metals are visible in the electron microscope, these methods of study were combined with electron microscopy.[3–5]

The distribution of adenosinetriphosphatase (ATPase) and adenosinediphosphatase (ADPase) activity has been described in normal rat brain using frozen sections which were prepared from tissue blocks that were fixed in formol-calcium.[6] ATPase activity was localized on the cell membranes of many neurons, on the neuroglia, and in both smooth muscle and endothelium of the blood vessels. The substitution of adenosinediphosphate (ADP) for adenosinetriphosphate (ATP) in the incubation medium resulted in a similar localization except that no neuronal activity was present. In the frozen sections, only diffuse capillary staining was noted. These thick sections did not permit accurate visualization of the capillary basement membrane. Therefore, we hoped that the application of the electron microscope to the study of these vascular structures would reveal more accurate localization of ATPase activity.

Methods and Materials

Fresh normal mouse, rat, and rabbit cerebrum, mouse cerebellum, mouse and rabbit choroid plexus, and mouse kidney were employed. This tissue was quickly cut into 1-mm. cubes. Some blocks were fixed in 1% osmium tetroxide buffered with veronal acetate for a period of seven minutes. Most of the tissue was fixed in formol-calcium which was maintained at 4° C. overnight. After fixation, the blocks of tissue were incubated in the medium of Wachstein and Meisel[7] for fifteen, thirty, and forty-five minute intervals; one group of tissue blocks was incubated for fifteen minutes in a medium in which ADP was substituted for ATP. That tissue which was initially fixed in osmium tetroxide was then postfixed in formol-calcium overnight. The tissue which was originally placed in formol-calcium was postfixed in 1% osmium tetroxide for ninety minutes. A series of experiments was performed with a thin coronal slice of mouse cerebrum fixed in formol-calcium overnight. A frozen section 20 μ in thickness was cut with a freezing microtome and was incubated in the Wachstein-Meisel medium for a period of fifteen minutes. This thin section was then cut into 1-mm. squares and was postfixed in osmium tetroxide for ninety minutes. Tissue controls were ob-

From the Lucy and Henry Moses Research Laboratories of the Laboratory Division, Montefiore Hospital, New York City.

This work was supported by Grant B-1944 from the National Institute of Neurological Diseases and Blindness.

*New address: Department of Anatomy, Yale University School of Medicine, New Haven, Conn.

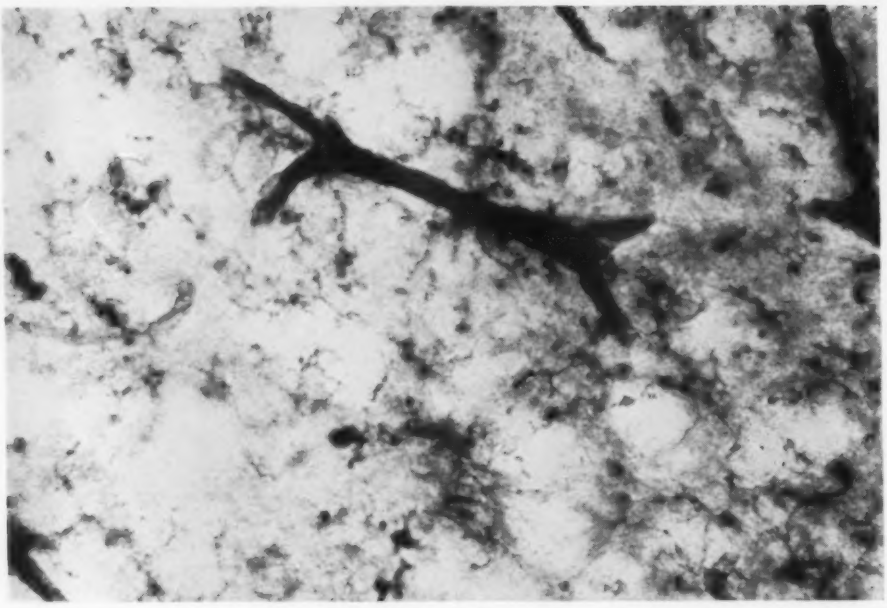


Fig. 1. Mouse cerebrum showing high ATPase acitivity in blood vessels. × 540

tained by incubation in a medium to which ATP was not added.

All these tissues were rapidly dehydrated in graded alcohols. They were embedded in a mixture of methyl and butyl methacrylate resin. Thin silver sections were cut using a Porter-Blum (Servall) ultra microtome. The sections were examined with an RCA, E.M.U. 3-D electron microscope.

Tissue was also obtained for study with the light microscope. These tissue slices were fixed in formol-calcium overnight. Frozen sections were cut with the freezing microtome and were incubated in the Wachstein-Meisel medium for an interval of twelve minutes. When ADP was used as a substrate, the incubation time was fifteen, thirty, and sixty minutes.

RESULTS

The light microscopic localization of ATPase activity in frozen sections of rat, mouse, and rabbit brain was similar to that which was previously described[6] (Fig. 1). The capillaries were heavily and diffusely stained. The substitution of ADP for ATP in the incubating medium resulted in similar vascular and neuroglial staining (Fig. 2). The neurons were not stained.

When the tissues were examined in the electron microscope, the formol-calcium fixation resulted in better preservation of fine structure and enzyme than did osmium tetroxide fixation. In addition, the osmium-fixed tissue contained much nuclear staining. The vascular structures in the brain were better preserved than the parenchymal tissue. The fine structure of neurons and neuroglia was largely destroyed. Much more fine structure remained in the kidney than in the brain. The following observations of ATPase activity in capillaries are from tissue which was fixed in formol-calcium.

The capillaries in the cerebrum and the cerebellum revealed localization of enzyme activity in 2 distinct layers (Figs. 3 and 4). This metallic deposition differed greatly from the nonspecific staining which occurred in the control series where no substrate was used (Fig. 5).

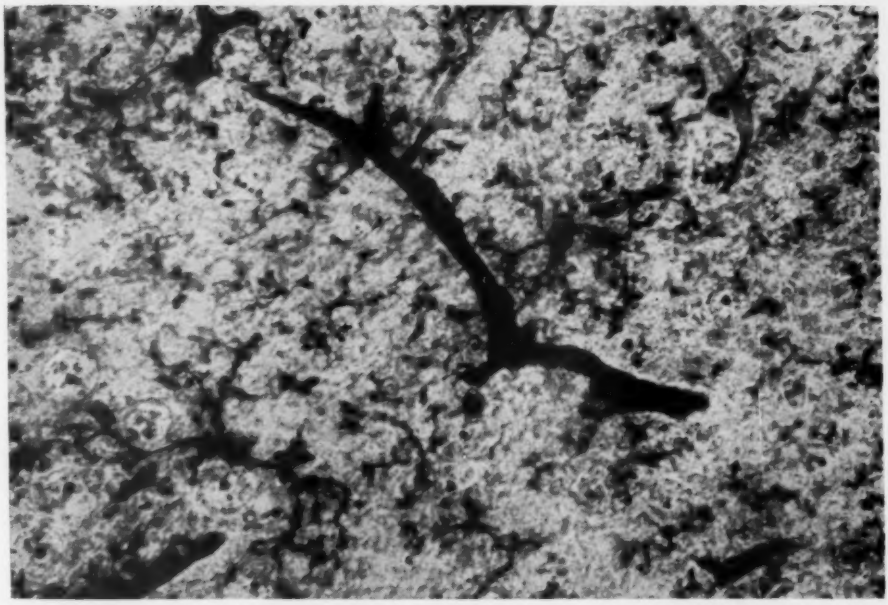


Fig. 2. Mouse cerebrum. Vascular and glial staining after use of adenosine diphosphate as substrate. × 540

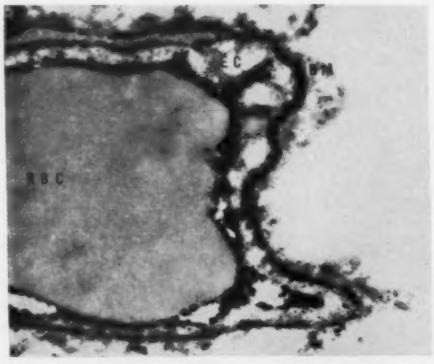


Fig. 3. ATPase activity in cerebral capillary. Outer layer of activity is in the basement membrane, which is identified by its characteristic splitting. BM=basement membrane. EC=endothelial cell. RBC=red blood cell. × 22,400

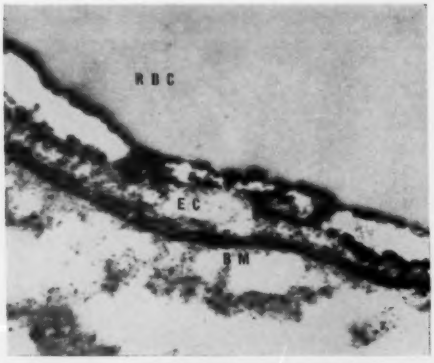


Fig. 4. Cerebral capillary which demonstrates ATPase activity in the basement membrane, in the endothelial cell, and in the red blood cell. BM=basement membrane. EC=endothelial cells. RBC=red blood cell. × 43,600

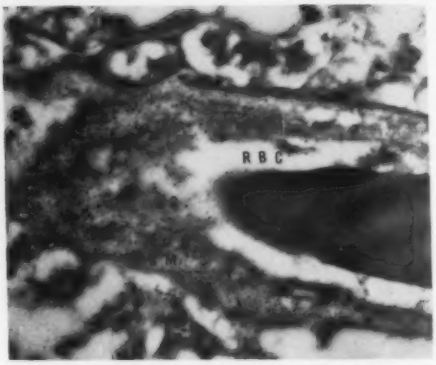


Fig. 5. Control section of a cerebral blood vessel showing presence of nonspecific lead. BM=basement membrane. EC=endothelial cell. RBC=red blood cell. × 22,400

The inner zone of activity was undoubtedly in the endothelial cell and appeared most intense near the luminal surface. This zone varied in intensity, and, occasionally, endothelial cells were seen which contained little enzyme activity. The outer layer was more consistent in staining intensity but was more difficult to localize. In those specimens which were incubated for fifteen minutes, this outer layer frequently divided and then continued as a double zone. The only structure in the vascular-glial complex which divides in this manner is the basement membrane. The basement membrane was identified as the site of enzyme activity in this part of the blood vessel wall. However, when the blocks were incubated for thirty and forty-five minutes, the basement membrane was often observed to be devoid of enzyme activity (Fig. 6). A peripheral zone of staining was present but appeared to be external to the basement membrane. Examination of the frozen section revealed an outer zone of enzyme activity which clearly divided (Fig. 7). Therefore, this area of activity was again localized in the basement membrane.

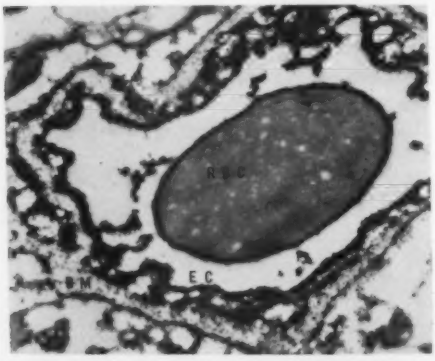


Fig. 6. Blood vessel in mouse cerebrum displaying diffusion of enzyme activity out of the basement membrane. BM=basement membrane. EC=endothelial cell. RBC=red blood cell. ×22,400

The choroid plexus was found to contain much ATPase activity in the epithelial cells and in the blood vessels. However, the capillaries contained only one zone of enzyme activity. This zone was clearly centrally located and was localized in the endothelial cell (Fig. 8). A similar distribution of ATPase activity was noted in the peritubular capillaries of the mouse kidney (Fig. 9).

In addition to localization within the capillary walls, there appeared to be a layer of enzyme activity on the surface of red blood cells lying within the capillary lumina. ATPase activity was not noted on the membranes of glial cells and Purkinje cells. When ADP was used as a substrate, vascular staining was observed which was similar to that seen after the use of ATP. Also noted was definite activity in glial cells which appeared localized at the peripheral cell membranes.

DISCUSSION

The technical aspects of electron histochemistry present many difficulties, of which tissue preservation is probably the most serious. Brain parenchyma is difficult to preserve well even with ordinary methods of fixation and embedding, and it is poorly preserved after histochemical technics. Fortunately, the blood vessels are more durable, and there is sufficient fine structure remaining in them to localize ATPase activity. Formol-calcium appears to be better than osmium tetroxide for preservation of brain fine structure and ATPase activity. However, improved fixation is necessary, especially for any investigation of neurons and neuroglia.

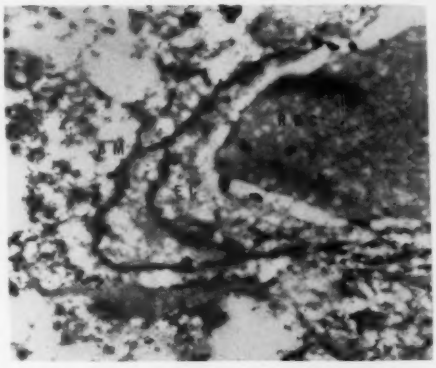


Fig. 7. Frozen section of cerebral capillary which demonstrates ATPase activity in the basement membrane. BM=basement membrane. EC=endothelial cell. RBC=red blood cell. × 22,400

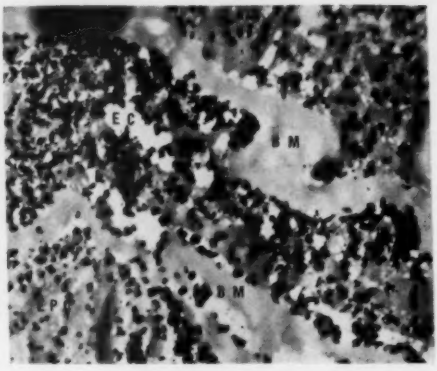


Fig. 8. Capillary in mouse choroid plexus which shows lack of enzyme activity in the basement membrane. BM=basement membrane. EC=endothelial cell. EPC=epithelial cell. × 22,400

Enzyme diffusion is a significant objection to the use of blocks of tissue in electron histochemistry; two forms of this phenomenon were observed. When osmium tetroxide is used as the initial fixative, false localization of enzyme activity in nuclei is frequently noted. With prolonged incubation times, after formol-calcium fixation, enzyme diffusion was observed out of the basement membrane. At this time, the use of frozen sections appears to be the most satisfactory technic for accurate localization of enzyme activity.[8] Tissue blocks have the advantage of affording better preservation of structure and enzyme, as well as providing ease of handling during fixation and embedding. Therefore, it is preferable to work mainly with tissue blocks while using frozen sections as a control.

Sectioning of the tissue entails a technical problem which was also emphasized by Essner, Novikoff, and Masek.[5] Only the most superficial part of the block was adequate in our experiments for an investigation of this type.

The dual localization of ATPase activity in the basement membrane in addition to the endothelial cell is a unique characteristic of brain capillaries. We confirmed previous light microscopic and electron microscopic observations of peritubular capillaries of the kidney which revealed ATPase activity only in the endothelial cell.[8,9] The basement membrane is also devoid of enzyme activity in the choroid plexus. Choroid plexus capillaries and renal peritubular capillaries have been compared by several authors.[10,11] Both have endothelial cells which often fail to form complete linings, whereas capillaries of the brain are always lined completely with endothelial cells.

The capillaries of brain parenchyma are most distinguished by their limited permeabil-

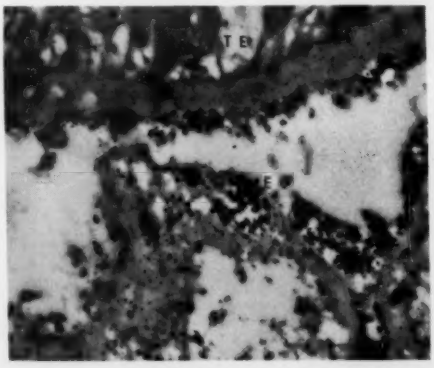


Fig. 9. Mouse kidney with a peritubular capillary containing no ATPase activity in the basement membrane. BM=basement membrane. EC=endothelial cell. TE=tubular epithelium. × 22,600

ity to certain electrolytes and vital dyes. This peculiarity is often referred to as the blood-brain barrier. The capillaries in the choroid plexus and the peritubular capillaries of the kidney possess no such selective permeability. It is quite possible that the distinct localization of ATPase in basement membranes of cerebral and cerebellar capillaries is correlated with the blood-brain barrier.

ATPase activity may be a manifestation of an in vitro functional disorder of enzyme involved in oxidative phosphorylation. Although appearing to be hydrolytic, its true function may be transphosphorylative.[12] The presence of both ATPase and ADPase activity at similar sites in the capillary wall suggests that either two distinct enzymes exist or that a single apyrase is present which is capable of hydrolyzing both ATP and ADP.

The presence of this enzyme activity in the basement membrane provokes speculation on the possible function of this structure in transfer dynamics. Palade[13] has recently proposed that the basement membrane has significant control over capillary permeability. He suggests that the endothelial cell mainly regulates the amount of material presented to the basement membrane for transfer. The localization of a high energy–producing enzyme, such as ATPase, in the basement membrane enhances the idea that it actively controls capillary permeability. Its presence in capillaries in which there is marked limitation of vascular permeability appears to imply that it is closely linked with such control.

CONCLUSION

1. The use of formol-calcium as an initial fixative is more suitable than osmium tetroxide for the study of ATPase activity in the brain.

2. Enzyme diffusion complicates the use of tissue blocks for electron histochemistry. The length of incubation and type of fixation are factors involved in this phenomenon. Frozen sections appear to be the best available control technic.

3. An electron microscopic examination of cerebral and cerebellar capillaries reveals a localization of ATPase in the basement membrane and endothelial cell.

4. The capillaries of the choroid plexus contain ATPase only in the endothelial cells. This lack of enzyme in the basement membrane is similarly found in the peritubular capillaries of the kidney.

5. The dual localization of ATPase activity in the basement membrane and in the endothelial cell is noted in vascular structures which are singularly characterized by limited permeability to electrolytes and vital dyes (blood-brain barrier). This anatomic fact may have important functional significance.

6. The presence of enzyme activity in the basement membrane indicates that this structure may be important in transfer regulation by cerebral capillaries.

REFERENCES

1. Torack, R. M., Terry, R. D., and Zimmerman, H. M.: The fine structure of cerebral fluid accumulation I. Swelling secondary to cold injury. Am. J. Path. 35:1135, 1959.
2. Torack, R. M., Terry, R. D., and Zimmerman, H. M.: The fine structure of cerebral fluid accumulation II. Swelling produced by triethyl tin poisoning and its comparison with that in the human brain. Am. J. Path. 36:273, 1960.
3. Sheldon, H., Zetterqvist, H., and Brandes, D.: Histochemical reactions for electron microscopy: acid phosphatase. Exper. Cell Res. 9:592, 1955.
4. Brandes, D., Zetterqvist, H., and Sheldon, H.: Histochemical techniques for electron microscopy: alkaline phosphatase. Nature 177:382, 1956.
5. Essner, E., Novikoff, A. B., and Masek, B.: Adenosine triphosphatase and 5-nucleotidase activities in the plasma membrane of liver cells as revealed by electron microscopy. J. Biophys. & Biochem. Cytol. 4: 711, 1958.
6. Becker, N., Goldfischer, S., Shin, W., and Novikoff, A. B.: The localization of enzyme activity in the rat brain. J. Biophys. & Biochem. Cytol. In press.
7. Wachstein, M., and Meisel, E.: Histochemistry of hepatic phosphatases of a physiologic pH. Am. J. Clin. Path. 27:13, 1957.
8. Novikoff, A. B.: Personal communication.
9. Slater, H. W., Novikoff, A. B., and Masek, B.: Adenosine triphosphatase activity in the cell membranes of kidney tubule cells. J. Biophys. & Biochem. Cytol. 4:765, 1958.
10. Maxwell, D. S., and Pease, D. C.: The electron microscopy of the choroid plexus. J. Biophys. & Biochem. Cytol. 2:467, 1956.
11. Millen, J. W., and Rogers, G. E.: An electron microscopic study of the choroid plexus in the rabbit. J. Biophys. & Biochem. Cytol. 2:407, 1956.
12. Hess, H., and Pope, A.: Intralaminar distribution of adenosinetriphosphatase activity in rat cerebral cortex. J. Neurochem. 3:287, 1959.
13. Palade, G. E.: Personal communication.

Selective head cooling in the dog

A preliminary report of technic and results

William Lee Pritchard, M.D.

SELECTIVE HEAD COOLING as an experimental procedure was first reported by Jensen, Parkins, and Vars,[1] who described the use of an extracorporeal vascular shunt to cool carotid blood. They lowered brain temperature of dogs to levels below 20° C. within fifteen minutes from the beginning of perfusion. They stated that the limitations of such experiments appeared to be cardiac irritability due to low body temperature, as 3 of their dogs died of cardiac fibrillation or asystole. They also stated that differential head cooling for long periods of time in the range of 12 to 18° C. produced no neurologic deficits but that their animals subjected to cooling in the range of 8 to 12° C. were comatose, disoriented, or demonstrated motor ataxia.

Clinical trial of selective brain cooling was first reported by Kimoto, Sugie, and Asano,[2] who performed open heart surgery under direct vision with the aid of selective brain cooling by carotid shunt. Carotid perfusion with cooling was carried on for fifteen minutes, attaining brain temperature as low as 17 to 18° C. Acetylcholine was used to prevent ventricular fibrillation.

These studies demonstrated the facility of brain cooling by perfusion technic, illustrating well the rapidity with which low temperatures may be attained. It is also apparent that the use of a perfusion technic subjects the entire body to hypothermia. At present, perfusion hypothermia may be maintained for long periods of time only in conjunction with use of a pump oxygenator, as was most recently reported by Sealy and associates.[3] In the search for an alternative situation in which extended cerebral cooling might be obtained by a carotid perfusion technic without the use of a pump oxygenator, selective head cooling was accomplished by establishing a second extracorporeal perfusion unit by which the cold jugular blood returning from the head might be rewarmed before returning to the general circulation.

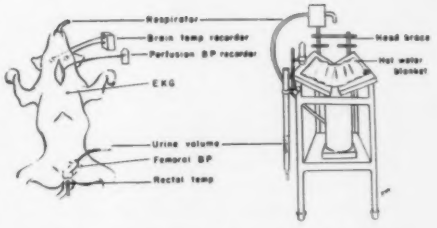


Fig. 1. Apparatus and experimental preparation

PROCEDURE

For the experiments, 23 dogs weighing 35 to 72 lb. were used. Endotracheal anesthesia of room air and Fluothane (Ayerst Laboratories) was administered in a nonrebreathing system with assisted respiration (Fig. 1). Urine output was recorded. Femoral pulse and blood pressure were monitored with a pressure transducer. Lead 2 of the electrocardiograph was recorded. A thermocouple was inserted into each hemisphere of the brain through twist drill holes in the skull. Thermocouples recorded temperature in the rectum and at 3 levels of the esophagus. Pulse and pressure of the carotid perfusion also were measured. All these parameters were recorded on an 8-channel Sanborn Polyviso Recorder.

From the Section on Pain, Surgical Neurology Branch, National Institute of Neurological Diseases and Blindness, Bethesda, Md., and the Department of Neurosurgery, Medical College of Georgia, Augusta.

The work carried on at the Medical College of Georgia was supported by Grant B-2342 from the National Institute of Neurological Diseases and Blindness.

Presented at the Southern Neurosurgical Society, February 1960.

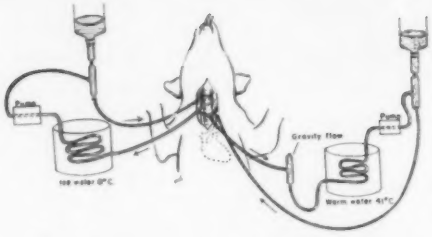


Fig. 2. Extracorporeal cooling and warming procedure

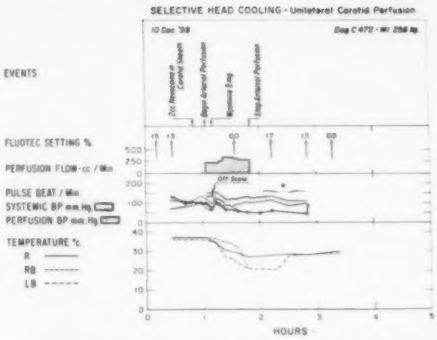


Fig. 3. Selective head cooling by unilateral carotid perfusion

After heparinization, one or both carotid arteries were cannulated (Fig. 2). The carotid outflow was shunted through a cooling system and then pumped into the distal carotid segment to the head. Jugular blood passed by gravity flow through a rewarming system and was then returned by pump to the superior vena cava, thereby rewarming the blood from the cold head before it returned to the systemic circulation.

On removal of the cannulas, the carotid arteries were repaired or ligated and the jugular veins were ligated.

RESULTS

In 23 experiments, there were 10 deaths (Table 1). In the group of animals subjected to carotid perfusion only, there were 2 deaths due to mechanical difficulties: 1 due to anoxia caused by inadequate ventilation and death, and the second due to massive air embolism to the brain which was recognized at the time of the perfusion. Ventricular fibrillation during the perfusion caused 3 deaths. In the second group, those with cooling plus jugular rewarming, 2 deaths were due to congestive heart failure. Both had worms in the right side of the heart with cardiac dilation. Severe intracranial hemorrhage occurred in 3 animals, rendering them decerebrate before death. The bleeding in these animals probably occurred during the placement of the thermocouples into the brain.

TABLE 1

CAUSES OF EXPERIMENTAL DEATHS

	Cause	
Carotid cooling only	Respirator difficulty	1
	Massive air embolism	1
	Ventricular fibrillation	3
Carotid cooling and jugular warming	Cardiac failure due to heart worms	2
	Intraventricular hemorrhage	3
	Total	10

The 13 animals that survived again fall into 2 groups, those which had only carotid cooling and those which had carotid cooling combined with jugular rewarming. The typical record (Fig. 3) of the first type of experiment shows the beginning of arterial perfusion with temperatures in the normal range. A rapid decline of the brain temperature to 18° C. in the brain occurred in eighteen minutes. The systemic temperature also declined to 26.9° C. rectally, at which point the carotid perfusion was stopped. Thereafter, rectal temperatures rose, as did the brain temperatures. The total perfusion time, fifty-three minutes, was the longest of this group. After brain cooling had progressed satisfactorily, anesthetic was not needed. The systemic pulse and blood pressure gradually declined as the systemic temperature declined; 5-mg. doses of Wyamine seemed to protect the heart from the low temperature.

In a representative experiment of bilateral carotid cooling and jugular warming (Fig. 4.), there was a rapid drop in brain temperature to 20° C. within twenty-four minutes from the onset of perfusion. Thereafter, the decline in temperature was less rapid. Rectal tempera-

ture declined but was maintained in this animal at levels of above 30° C. This procedure lasted for three hours of active perfusion. Near the end of the experiment, there were spontaneous movements characteristic of the decerebrate state, with spasticity and flexor withdrawal, which resolved at the end of the procedure as brain temperatures returned to levels above 30° C.

In the first group of animals subjected only to carotid cooling, perfusion times ranged from eighteen to fifty-three minutes, with an average of thirty-seven minutes (Table 2). The lowest temperatures achieved ranged from 10.5 to 26° C., with an average of 17° C. In the second group of animals, in which carotid cooling and jugular rewarming were carried out, perfusion time ranged from one hour fourteen minutes to three hours, with an average ot two hours forty-three minutes. The lowest brain temperatures attained ranged from 6.1 to 14°, with an average of 9.5° C. The lowest body temperatures ranged from 29.5 to 35.4° C., with an average of 31.8° C.

Observation of the animals that survived this procedure revealed no neurologic deficits. The immediate postoperative course corresponded to that of any animal awakening from a general anesthetic of similar duration. The animals were up and able to take nourishment within twelve hours; one dog died of distemper nine days postoperatively. The remaining dogs were observed for periods of four to ten weeks.

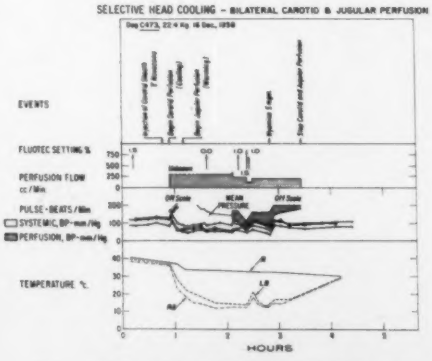


Fig. 4. Selective head cooling by bilateral carotid and juglar perfusion

TABLE 2

LOWEST TEMPERATURES ATTAINED DURING PERFUSION

	Perfusion time	*Brain*	*Rectal*
Carotid cooling only (5 survivors)	18 to 53 minutes (37 minutes)*	10.5 to 26° C. (17° C.)	26.2 to 30.9° C. (28.5° C.)
Carotid cooling and jugular warming (8 survivors)	1 hour 14 minutes to 3 hours (2 hours 43 minutes)	6.1 to 14° C. (9.5° C.)	29.5 to 35.4° C. (31.8° C.)

*Figures in parentheses are averages.

The dogs were then sacrificed by rapid exsanguination. The brain was removed and placed in 10% formalin solution; 4 brains were chosen from among the survivors of bilateral carotid cooling and jugular rewarming. Examination of representative sections revealed no brain damage. Specifically, there were no demonstrable neuronal changes or astrocytic proliferation. The pathologic studies corroborate the clinical course in establishing that the brains of these animals were not damaged by being subjected to extremely low temperatures during these procedures.

DISCUSSION

At present, we are primarily interested in reporting the technic and preliminary study of selective head cooling. Several advantages of this technic may promise to make it applicable in clinical neurosurgery.

The rapidity with which brain cooling can be accomplished by this technic may lend itself to treatment of traumatic or anoxic insults to the brain, as it has been shown that suitable hypothermic levels must be attained within ninety minutes after such injury in order for this to be an effective treatment.[4]

Control of not only brain temperature but also brain circulation is inherent in this technic and may be a highly effective adjunct to surgery of intracranial vascular lesions.

Selective head cooling with maintenance of relatively normal body temperature promises to afford protection and to obviate undesirable effects of total body hypothermia, such as cardiac arrhythmia and metabolic acidosis. Further development of this technic is planned to study these questions.

SUMMARY

1. A preliminary series of 23 experiments is described during which a technic was evolved for rapid and extreme cooling of the brain by an extracorporeal perfusion unit with rewarming of the jugular blood before its return to the systemic circulation, in order to avoid extremely low body temperature.

2. It was demonstrated that it is possible to carry out hypothermic perfusion of the head for a considerably longer period of time if jugular rewarming is used.

3. Except for deaths due to difficulties unrelated to hypothermia per se, animals subjected to this procedure survived without neurologic deficit or evidence of brain damage.

4. It is proposed to continue these studies in order to learn if this technic may be adapted to specific problems in neurology and neurosurgery in which selective brain hypothermia may be of benefit.

The author expresses his appreciation for the assistance of Dr. Hans Peters in preparing and studying the pathologic specimens, Mrs. Frances de Roller for the preparation of figures, and Mr. Sidney Downs for technical assistance in carrying out the experimental work.

REFERENCES

1. Jensen, J. M., Parkins, W. M., and Vars, H. M.: In Dripps, R.D., ed.: The Physiology of Induced Hypothermia. Washington, D.C., NAS-MRC Publication 451, 1956, pp. 271-274.
2. Kimoto, S., Sugie, S., and Asano, K.: Open heart surgery under direct vision with the aid of brain cooling by irrigation. Surgery 39:592, 1956.
3. Sealy, W. C., Brown, I. W., Young, W. G., Smith, W. W., and Lesage, A. M.: Hypothermia and extracorporeal circulation for open heart surgery. Ann. Surg. 150:627, 1959.
4. Rosomoff, H. L.: Conference on Hypothermia. New York City, New York Academy of Science, Section of Biology, November 1958.

Influence of surgical procedures on the course of multiple sclerosis

Alan Ridley, M.B. (Durh.), M.R.C.P. (Lond.),
and Kurt Schapira, M.B., B.S. (Durh.)

Deterioration or exacerbation of multiple sclerosis after operation has been seen occasionally by every neurologist. Intermittent deterioration is a familiar feature of the natural history of multiple sclerosis, and, since "spontaneous" exacerbation can be expected to occur on an average once every thirty months,[1] its frequency affords considerable opportunity for coincidence. Present evidence as to the probability of its occurrence after surgical intervention is inadequate to form a sound basis for practical advice about the risks of elective operations in patients with the disease.

The North-East Multiple Sclerosis Survey based at the Royal Victoria Infirmary, Newcastle upon Tyne, afforded an opportunity for the collection of information on this point. Of 662 patients examined, 40 had undergone 57 operations under general anesthesia in various hospitals since the onset of the neurologic disorder. In 3 further patients operated on under local anesthesia (2 for nasal polyps and 1 for a ganglion of the wrist), operation was apparently without influence on the course of the condition. These 3 cases are excluded from further discussion.

The age distribution of the 40 patients who had undergone operation was similar to that of the total surveyed. A preponderance of female patients (31:9) was related to the high proportion of gynecologic operations concerned (21, including 10 for cervical dilation and curettage and 5 hysterectomies). Of the remaining 36 operations, 10 were abdominal (appendectomy 4, gastrectomy 4, and hernia 2), 22 miscellaneous, and 4 dental. Most operations had been carried out after omnopon and scopolamine premedication followed by thiopental, nitrous oxide and oxygen, and sometimes Trilene. In the 33 cases in which they were available, the anesthetic records revealed no untoward reactions.

The immediate effect of operation was assessed by comparing the grade of disability immediately before operation with that obtaining one month later. A simple grading of disability was employed: Grade I, no symptoms and no disability; Grade II, symptoms without disability; Grade III, disability causing some restriction of activity, and Grade IV, activity markedly restricted. During the postoperative month, no acute exacerbations of the neurologic disorder were observed after any of the 57 operations. In 47 instances, no measurable effect on disability could be detected; 2 patients showed improvement with an upward change of grade, while 8 showed deterioration. In 4, this was definite, with a downward change of 1 grade in 3 cases and of 2 grades in 1. In the other 4 cases, deterioration was insufficient to constitute a change of grade.

The 8 operations that were followed by deterioration were total hysterectomy (2), gastrectomy, dilation and curettage, ischiorectal abscess, inguinal hernia, ligature of varicose veins, and radium menopause. Of the 8 instances of deterioration, 2 occurred in the same patient—after herniotomy in 1945 and after hysterectomy in 1947; however, hemorrhoidectomy in 1951 left the same patient unscathed. Neurologic status was unaffected after 3 of 4 gastrectomies and 3 of 5 hysterectomies. The only patient whose condition deteriorated after dilation and curettage had survived a similar operation four years

From the Department of Neurology, Royal Victoria Infirmary, Newcastle upon Tyne, England.

previously without ill effect, as did the 8 other patients subjected to this operation. No relation could be demonstrated between the duration of confinement to bed and liability to subsequent deterioration. No operations had been performed in patients under the age of 29 years in this series, but the age distribution of deteriorating cases appeared to parallel that of the group as a whole.

Any possible long-term influence of operation on the natural history of multiple sclerosis is even more difficult to assess than an immediate effect. In these 57 instances of surgical procedures under general anesthesia, the disability was graded immediately before operation, twelve months previously, and twelve months postoperatively. In 40 cases, disability was static over this two-year period. During the year following operation, 2 patients whose disability was static during the twelve preoperative months showed improvement. During the two-year period, 15 cases deteriorated; 4 of these became worse during the preoperative year, remaining unchanged postoperatively, while 11 had deteriorated at the end of the postoperative year. Of the latter, 3 had also deteriorated preoperatively, 8 remaining unchanged during the year preceding operation. These figures are not easy to interpret and are too small to be statistically significant. However, the fact must be recorded that, in 8 of 57 instances, the condition appeared to be static at the time of operation but showed deterioration twelve months later. Of these cases, 6 are among the 8 previously noted as showing deterioration during the postoperative month.

COMMENT

The number of cases analyzed is small. It could be doubled by adding patients from outside the survey, among whom we have encountered acute exacerbation in the immediate postoperative period. The inclusion of such "selected" cases would, however, vitiate the representative nature of the present series and any limited value it may have in permitting an assessment of risk.

Briefly, the lesson of these findings seems to be that, while there is suggestive evidence that surgical procedures—perhaps especially major operations—are sometimes followed by deterioration in the neurologic condition of patients with multiple sclerosis, this is probably less frequent than has often been suggested. Even if we exclude from our consideration the patients apparently "improved" by operation, postoperative deterioration is probably not seen in more than 14% and, in some of these, it is transient. It must be remembered also that a proportion of these cases would almost certainly have deteriorated in any case. Our findings appear to furnish little justification for the avoidance of surgical intervention in patients with multiple sclerosis when this is clearly indicated on its own merits.

The authors are indebted to the North-East Multiple Sclerosis Trust and to the Board of Governors of the Royal Victoria Infirmary for financial support and to Dr. Henry Miller for suggesting the nature and scope of the investigation.

REFERENCE

1. McAlpine, D., Compston, N. D., and Lumsden, C. E.: Multiple Sclerosis. Edinburgh, Livingstone, 1955

Fatal nucleus pulposus embolism of spinal cord after trauma

J. Lawrence Naiman, M.D., William L. Donohue, M.D., and John Stobo Prichard, M.D.

A POSTMORTEM INVESTIGATION of the sudden death of an adolescent boy shortly after a basketball game disclosed presumptive evidence as to the cause of his death which was so unusual that a report seems warranted.

The essential lethal lesions were multiple microscopic arterial emboli of nucleus pulposus material involving a considerable segment of the spinal cord and the adjacent brain stem. These were associated with microscopic hemorrhages within the cord substance. No similar case has been found in a review of the literature of the past twenty-five years.

CASE REPORT

L. M., a 15-year-old boy, was active and in good health on the morning of March 3, 1959. The following is the sequence of events which terminated in his death within three hours.

8:15 a.m. A preclass basketball practice was organized in the school gymnasium with an instructor in attendance.

8:30 a.m. As the result of a collision with another boy who was attempting to remove the ball from his grasp, the patient was thrust backwards to the floor, landing on his buttocks and then on his right shoulder. Although the impact was regarded with some concern by observers, the boy did not complain of any undue pain at this time. He was able to rise almost immediately and continue playing until the end of the game ten minutes later.

8:50 a.m. While sitting at his desk in class, he complained of a sudden severe pain in the epigastrium which caused him to double up. In the next ten to fifteen minutes, the pain shifted to his back, neck, and shoulders. These pains gradually subsided after the boy was taken to the school principal's office and assisted to a couch.

9:10 a.m. After requesting a drink of water, he found that he was unable to lift the glass to his mouth. In the forty-five–minute interval before arrival of the parents and an ambulance, the boy had progressive weakness of all four extremities. This was associated with increasing difficulty in breathing.

10:15 a.m. He arrived at the Emergency Department of the Hospital for Sick Children with his parents, who at that time were unaware of the history of injury at school. Although conscious, he was critically ill and ashen gray, with slow, shallow respirations. The radial pulse was slow and weak, and the blood pressure unobtainable. After intratracheal intubation and administration of oxygen under positive pressure, his color improved considerably but he was unable to sustain respiration without assistance. Blood pressure was restored and maintained at normal levels with an intravenous infusion of 4 cc. of levarterenol bitartrate in 250 cc. of dextrose in water.

11:00 a.m. After stabilization of respiratory and circulatory functions, a more detailed neurologic examination was carried out. At this time, the boy was conscious and able to respond to questions by movements of his head. The cranial nerves and optic fundi were normal. Complete flaccid paralysis and loss of reflexes were present in all limbs. Respiratory paralysis was complete except for slight movement of the abdominal musculature. Sensory testing revealed a level of analgesia extending up to T3-T4 on both sides. The provisional diagnosis was a lesion in the cervical region of

From the Department of Pathology and Pediatrics, Hospital for Sick Children, Toronto, and the University of Toronto. Read at the twelfth annual meeting of the American Academy of Neurology, Miami, April 29, 1960.

the spinal cord, either a hematomyelia or a transverse myelitis.

11:30 a.m. Because of increasing difficulty in maintaining respirations, it was decided to transfer the boy to the operative recovery room where a mechanical respirator could be connected to the airway. However, before this could be carried out, it was found that his heart had stopped beating.

11:35 a.m. The patient was pronounced dead.

POSTMORTEM FINDINGS

The autopsy (A. 76/59) was performed two hours after death. At this time, the causal relation of the supposedly minor trauma was minimized. However, a preautopsy roentgenogram of the cervical spine had been taken, which was reported as normal. As most of the findings were entirely negative, only those germane to the cause and mode of death will be described.

The body was that of a tall, thin, well-developed boy. No abrasions or contusions were found. Before the start of the autopsy, a lumbar puncture was performed, which yielded clear cerebrospinal fluid with no cells and a normal protein concentration. The thoracic cavity and the organs therein were normal except for the tracheobronchial tree and lungs. The trachea and bronchi contained a large amount of pink, frothy fluid. Both lungs were heavy and edematous. On cut surface, each exuded a pink, frothy fluid similar to that in the trachea and bronchi; there were no areas of collapse or pneumonic consolidation. The abdominal cavity and its contents were entirely normal. No abnormalities were noted in the aorta or its branches throughout its length. After removal of the thoracic and abdominal viscera, the spine was examined for any gross abnormalities; none was obvious. The brain and entire spinal cord were removed together. No gross lesions were apparent before fixation. A detailed examination of the spinal canal after removal of the cord was not done. However, there were no abnormalities obvious enough to attract attention to this area.

Gross examination of sections of the brain and cord after fixation in 10% formalin was within normal limits. The small hemorrhages found in the microscopic sections were not visible to the naked eye; 9 sections were taken from representative areas of the brain. In addition, sections were taken at 16 levels of the spinal cord from the first cervical to the second sacral segment.

On microscopic examination, sections from all of the viscera were normal with the exception of the lungs, which showed acute pulmonary edema. No intravascular material, such as that described below, was found except in the areas specifically mentioned.

The most striking abnormality on microscopic examination of the spinal cord was multiple, small, fresh hemorrhages that were in greatest concentration in the gray matter. Although they were most numerous in the midcervical region, some hemorrhages were present at all levels of the spinal cord examined. In addition to the hemorrhages, there were fragments of a foreign substance which was in all respects identical to nucleus pulposus material within the lumina of the arterioles in a number of sections (Figs. 1 through 4). In the routine hematoxylin and eosin sections, this consisted of cartilage cells, connective tissue cells, and numerous concentrically arranged basophilic granules of varying size, embedded in a pale grayish-blue fibrillary matrix. These emboli were present in the lower medulla and in 10 sections of the spinal cord from C2 to T7. Their presence within the arteries in the anterior sulcus, in the small branches at the surface of the ventral portion of the cord, and in the central gray matter corresponded to the distribution of the anterior spinal artery (Fig. 5). In the medulla, the embolus was situated in a paramedian arteriole. No evidence of edema, nerve cell degeneration, demyelinization, or inflammatory reaction was found.

The key issue in the determination of the presumptive cause of death in this boy was the proof that arterial emboli did exist in the cord and the nature of the embolic material. In regard to the former, there can be no doubt that the material present in the small arteries and arterioles of the cord was obviously foreign to that locality. It was present in no other tissue and was associated with fresh petechiae. In addition, the clinical picture fitted perfectly with the areas of the cord and medulla involved. Periodic acid–Schiff, iron-

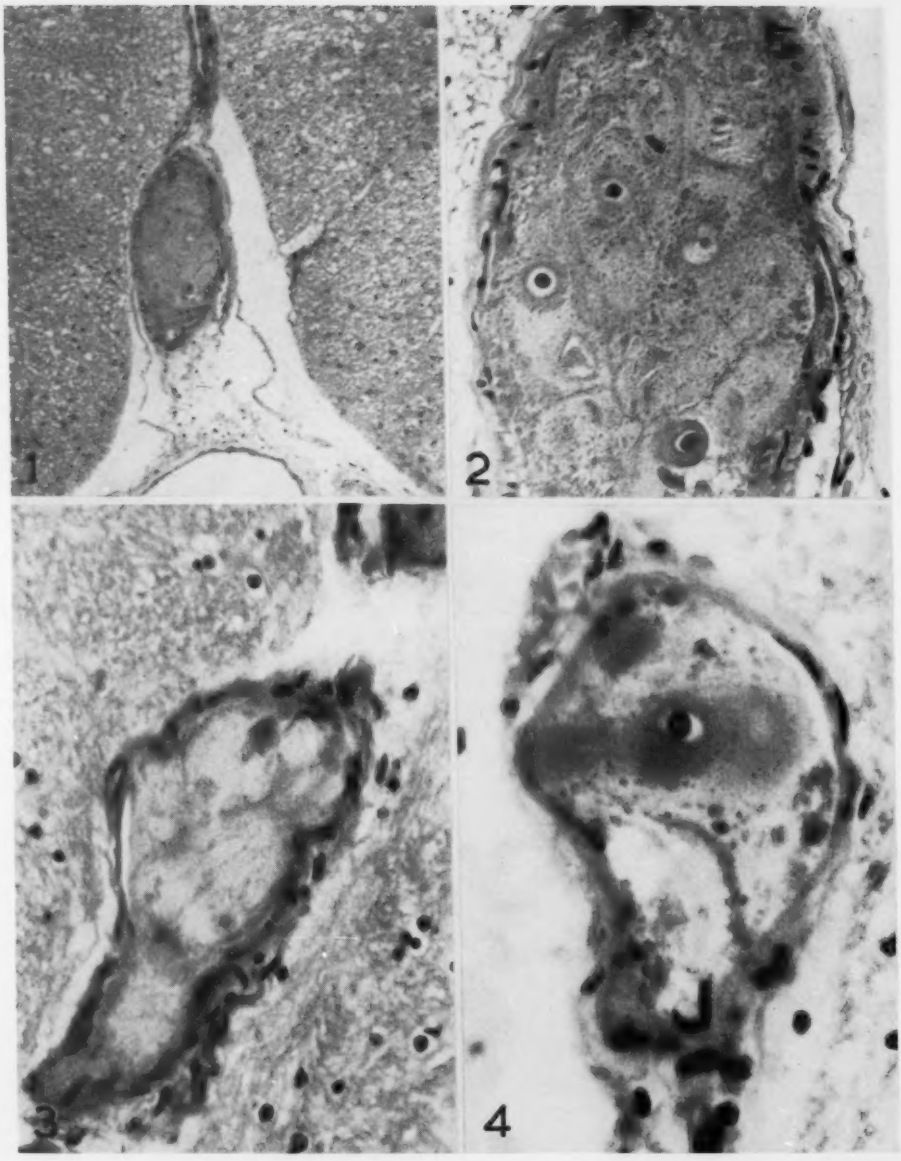


Fig. 1. Section of spinal cord at level of C2, showing embolic material filling lumen of anterior spinal artery in ventral median fissure. Hematoxylin and eosin. × 100

Fig. 2 Higher magnification of section in Figure 1, illustrating detailed morphology of nucleus pulposus material. Hematoxylin and eosin. × 640

Fig. 3. Embolus within paramedian artery in lower medulla. Hematoxylin and eosin. × 640

Fig. 4. Section of spinal cord at level of C2, showing embolus in small arteriole in gray matter. Iron-hematoxylin-safranin. × 940

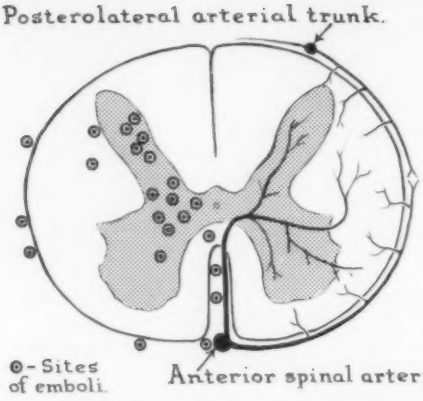


Fig. 5. Spinal cord, with composite representation of emboli on the left and corresponding distribution of anterior spinal artery on the right

hematoxylin-safranin, and alcium blue stains indicated the identity of the staining reaction of the embolic material with that of the nucleus pulposus. In view of the unusual nature of the findings, the microscopic preparations were shown to a number of senior pathologists, all of whom concurred with our conclusions.

DISCUSSION

Although the mechanisms producing the lesions in the spinal cord are not understood, the development of the clinical picture and the pathologic observations leave little doubt that the cord damage was the result of multiple microemboli of nucleus pulposus to the cord and was directly related to the minor trauma. In all probability, the embolism took place by way of the anterior spinal artery.

On the basis of the available information, it is not possible to formulate with certainty the exact pathway of the embolic material from the intervertebral disk to the anterior spinal artery. However, certain conclusions can be drawn from a knowledge of the anatomy of the spinal arteries.[1] The anterior spinal artery is formed in the medulla by union of branches of the vertebral arteries. It descends in the ventral median fissure and is augmented by a succession of small spinal (radicular) branches that enter the vertebral canal with the nerve roots through the intervertebral foramina; these branches are derived from the vertebral, ascending cervical, posterior intercostal, and lumbar arteries. Only about 6 to 8 of these radicular arteries actually contribute to the blood supply of the spinal cord. The largest of these vessels is found in the lumbosacral region and the next in order in the cervical region. The single anterior spinal arterial trunk extends the length of the cord. However, its caliber varies; it is greatest in the lumbosacral region, next in size in the cervical, and smallest in the thoracic region. Approximately the ventral two-thirds of the spinal cord is supplied by branches from this anterior spinal artery and the dorsal one-third from the smaller paired posterolateral spinal arteries.

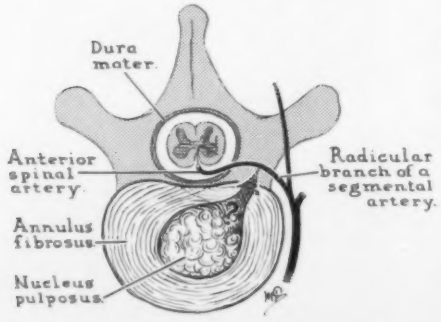


Fig. 6. Relationship of nucleus pulposus to spinal cord, illustrating possible site of entry into spinal arterial system

By what means might nucleus pulposus material enter the anterior spinal artery as a result of trauma? These 3 possibilities come to mind:

1. An injury with rupture of an annulus fibrosus. Lateral rupture of the annulus fibrosus and tearing of the adjacent radicular artery could result in extrusion of fragments of nucleus pulposus into the spinal arterial system. This injury might be produced by transient vertebral subluxation (Fig. 6).

2. An injury in which the annulus fibrosus remains intact. Although the nucleus pulposus is usually considered to be an avascular structure, in the child small blood vessels have been described which may persist until adolescence.[2] The sudden increase in intradisk pressure might conceivably result in "injection" of one

of these vessels and retrograde pulsion into a radicular artery and thence to the anterior spinal artery (Fig. 6). A similar mechanism might operate through a Schmorl node protruding into the body of a vertebra.

3. A third possibility is an anomalous vascularity, with or without an abnormal anastomsis of the arteries adjacent to or in one of the intervertebral disks. Unfortunately, at the time the autopsy was done, a detailed examination of the spinal bed from which the cord was removed was not undertaken; therefore, the possibility of such an anomaly cannot be established.

The pathologic effects of the nucleus pulposus embolism in this case are comparable to those seen in fat embolism of the central nervous system. Scattered petechial hemorrhages in the gray matter were the only discernible lesions. The absence of histologic evidence of neuronal degeneration is compatible with the short time of survival after the injury.

With a knowledge of the pathologic disturbance, a better understanding of the clinical picture is possible. The initial latent period between injury and onset of symptoms is consistent with the time necessary for nucleus pulposus material to disseminate through the spinal arterial system and produce the effects of cord ischemia. The early history of abdominal pain rapidly spreading to the back, neck, and shoulders can be attributed to the irritative effect of the scattered petechial hemorrhages on the nerve fibers along the crossed sensory pathway from the posterior horn to the lateral spinothalamic tract. Subsequent respiratory weakness, quadriplegia, and sensory loss would result from functional ischemic injury to the corresponding anterior horn cells and pyramidal and spinothalamic tracts in the ventral portion of the spinal cord supplied by the anterior spinal artery. The circulatory disturbances that terminated in cardiac failure and acute pulmonary edema can be ascribed to ischemic damage to the vital centers by the arterial embolism in the medulla. It is likely that, in the absence of this latter complication, the boy might have survived after the establishment of adequate pulmonary ventilation.

In a review of the literature of the past twenty-five years on the vascular complications of diseases and injuries of the intervertebral disk and spinal cord, no previous case reports of nucleus pulposus embolism of the spinal cord were found, nor was there any mention of this mechanism among the numerous causes of arterial infarction of the spinal cord listed in the recent review by Peterman, Yoss, and Corbin.[3] The importance of vascular insufficiency of the brain stem and spinal cord in spinal trauma was stressed by Schneider and Crosby[4] in a recent report, but postmortem examination in one of their cases showed no evidence of arterial occlusion by thrombosis or embolism. The absence of previous reports indicates that embolism of nucleus pulposus material is a rare condition. Since the appearances of the emboli in this case are so unusual and characteristic, it is unlikely that they could be overlooked unless a microscopic examination of the cord is omitted. Embolization of an extent permitting survival may explain some cases of the clinical syndrome of occlusion of the anterior spinal artery which follow trauma. It is hoped that an awareness of this lesion in the investigation of fatal cases of spinal cord injury may lead to the discovery of similar cases and perhaps shed light on the exact mechanism of the embolism.

SUMMARY

A case is presented of a 15-year-old boy who died shortly after a minor injury with progressive quadriplegia, respiratory paralysis, and sensory loss. Autopsy disclosed multiple microemboli of nucleus pulposus material in the arteries of a large segment of the spinal cord and medulla. The exact mechanism of this embolism is not known.

REFERENCES

1. Ranson, S. W., and Clark, S. L.: The Anatomy of the Nervous System. 10th ed. Philadelphia, W. B. Saunders Co., 1959, pp. 83-85.
2. Smith, N. R.: The intervertebral discs. Brit. J. Surg. 18:358, 1931.
3. Peterman, A. F., Yoss, R. E., and Corbin, K. B.: The syndrome of occlusion of the anterior spinal artery. Proc. Staff Meet. Mayo Clin. 33:31, 1958.
4. Schneider, R. C., and Crosby, E. C.: Vascular insufficiency of brain stem and spinal cord in spinal trauma. Neurology 9:643, 1959.

Announcing

Chartered Air Transportation for Members of the American Academy of Neurology

The Officers and the Board of Trustees of the American Academy of Neurology have given their approval to a proposal that the members of the Academy be solicited concerning their desire to form a group which will charter air transportation to and from the various neurological congresses which are to be held in Europe in 1961.

The American Academy of Neurology under no circumstances can assume responsibility for such arrangements but it has authorized the Treasurer, Dr. Charles M. Poser, to conduct such solicitation and make the necessary arrangements with a travel agency. This offer will apply only to members of the American Academy of Neurology and their immediate families.

The cost of a charter flight is determined by dividing the cost of the aircraft by the number of people in the plane. This includes children over the age of two who, therefore, must pay full fare. Children under the age of two go free. In order to obtain the lowest rate, all seats should be full. In the event that the response is such that total plane loads are incomplete, assignments will go to those who reserve first. The requests will be taken in order according to the postmark date.

It is proposed that air transportation be chartered between New York and Paris, Paris being most centrally located since the meetings will be held in Munich (neuropathology) and Rome (neurology, neuroradiology, EEG, genetics, etc.).

Alternate suggestions, including departure from the West Coast over the polar route will be entertained.

Since many members will want to combine this with vacations, it is suggested that the group depart from New York on or about September 1, 1961, and return from Paris on or about September 30, 1961.

Use of DC-7 equipment will result in the cost of approximately $280.00 per person round trip, while jet equipment will raise it to approximately $350.00 per person round trip. The cost is naturally determined by the number of people, as explained above, the aircraft being rented as a unit.

Our final contract with the airline must be signed two months before actual departure date. It will, therefore, be necessary that the full price be paid in advance. Many airlines also require that a 10% deposit be paid at the time that the actual equipment and date of departure have been decided upon. Every participant in this project must sign up for a round trip.

A down payment of $50.00 per person will have to accompany the signed request for reservations. This deposit will naturally be refunded should the number of participants be insufficient to arrange for at least one charter plane load to and from the meetings. This deposit will also be applied to the 10% deposit required and the full payment.

Members of the Academy who are interested are requested to fill out the attached questionnaire which is to be considered to be a request for a reservation and return it with their deposit fee as soon as possible prior to January 1, 1961.

Please fill in form below and return to:

CHARLES M. POSER, M.D., Treasurer, A.A.N.
University of Kansas Medical Center, Kansas City 12, Kansas

REQUEST FOR RESERVATION OF CHARTERED AIR TRANSPORTATION TO CONGRESSES – SEPTEMBER 1961

(Please print or type)

Name: _____ Date: _____

Address: _____
Street City State

Are you listed in the 1959 edition of the A.A.N. Directory? Yes _____ No _____

Number of reservations requested: _____ Check enclosed for $ _____

- Departure will be from New York and return to New York.
- Please indicate if you prefer destination to be: PARIS LONDON ROME
- Please indicate if you would prefer return to be from: PARIS LONDON ROME
- Please indicate if you would prefer to leave from the West Coast via the polar route.
- It is suggested that departure date be on or about September 1 and return on or about September 30, 1961. Please indicate if you would prefer

a different departure date: _____

a different return date: _____

I agree to pay full round-trip price for all reservations (exact amounts will depend upon the equipment and the number of passengers per plane load) at least 2 months before actual departure date or at the time requested.

Ten per cent of the total fare may be requested as a deposit a few weeks after equipment and departure date have been decided. The enclosed deposit will be applied to the full payment.

Signature: _____

Neurology

BOOK REVIEWS

Intraspinal Tumors of Childhood

by Robert W. Rand and Carl W. Rand, 560 pp., Charles C Thomas, Springfield, Ill., 1960. $16.50.

The purpose of this monograph is to aid in the earlier and more accurate diagnosis of spinal cord tumors and to stimulate more extensive research into the pathogenesis and treatment of intraspinal tumors, particularly primary gliomas.

Detailed case histories of 72 children are presented. They are divided into appropriate groups. The diagnosis and treatment are discussed, and relevant literature is reviewed.

Anyone working in the field of pediatric neurology will appreciate this volume. It is extremely well illustrated, the bibliographies are very complete, and the many diagnostic pitfalls are stressed. The authors point out that intraspinal tumors are rare in childhood and that, for this reason, there has been little written in the past which has presented the whole subject. This work should stand for years as a standard reference book.

J.P.R.

Clinical Neurophysiology

by John Marshall, 296 pp., Charles C Thomas, Springfield, Ill., 1959. $8.

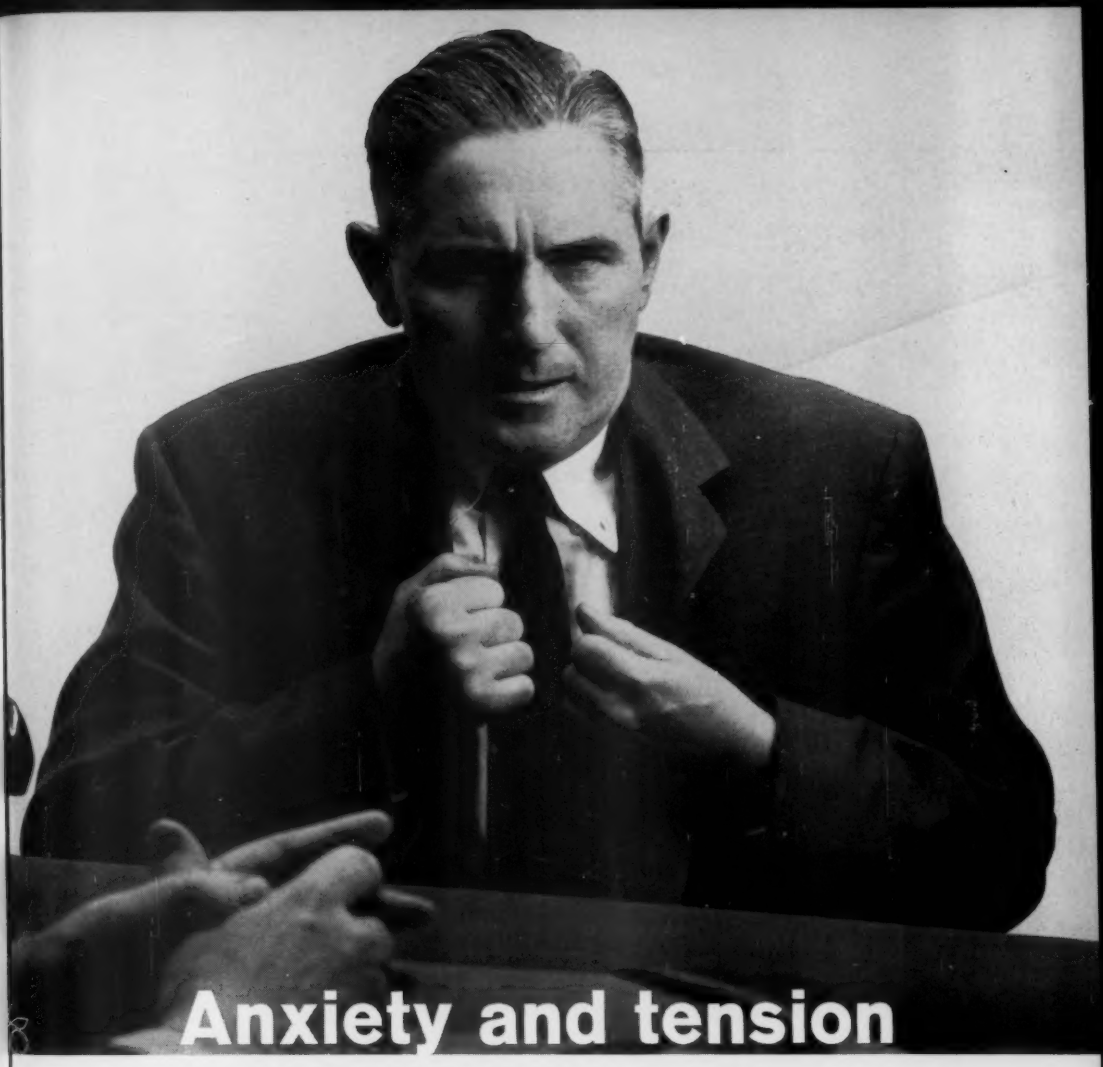
This concisely written book presents to the clinician relevant data on the physiology of the nervous system for practical utilization. It gives the neurologist the opportunity of integrating much basic information with his every day bedside observations. This is well illustrated in the exposition of the nature of the nerve impulse, where the ionic hypothesis is reviewed, the electrical accompaniments are described, and recent clinical applications are indicated.

In a similar manner, the present day knowledge of transmission at the neuromuscular junction is assembled and its relationship to myasthenia gravis is discussed. Following out the plan, the author describes the mechanical, chemical, and electrical aspects of muscular contraction and the clinical application in electromyography and other forms of electrodiagnosis. The topics that follow are equally informative: sensory neuron systems with particular reference to pain, including referred pain and visceral pain; transmission at the synapse, the reflex, and the role of acetylcholine; the activity of the isolated spinal cord and partial or complete transverse spinal lesions in man; the brain stem and decerebrate phenomena; and the cerebellum and cerebellar symptomatology.

There are discussions of the cerebral cortex and its electrical rhythm, the thalamus, the parietal lobe, the motor pathway and the present status of the Babinski sign, the rhinencephalon, hypothalamus, frontal and temporal lobes, and, finally, the auditory and visual systems.

This is a very readable book. It is too brief at many points to cover the extensive subject matter, but it is important to bear in mind it was not designed to be a textbook. It does quite well what it proposes to do: to set down background physiologic data for the clinical neurologist.

A.R.V.



Anxiety and tension

need not hinder therapy

EQUANIL *subtly encourages acceptance of therapy in many patients suffering mild and moderate neuroses. By relaxing mind and muscle—without impairing mental and physical acuity —it helps you help patients toward new insights. Very often,* EQUANIL *permits patients to return to normal day-to-day activities while undergoing therapy.*

EQUANIL is predictable in its actions. The efficacy of EQUANIL is thoroughly documented in hundreds of published clinical studies. Side-reactions are rarely encountered.

Although rare, allergic reactions may occur; dosage and quantity prescribed should be carefully supervised. For further information on prescribing and administering EQUANIL see descriptive literature, available on request.

Wyeth Laboratories Philadelphia 1, Pa.

Equanil®

Meprobamate, Wyeth

A Century of Service to Medicine

REVIEW COURSES IN BASIC and CLINICAL NEUROLOGY

April 24, 25, 26, 1961

Preceding the

1961 AMERICAN ACADEMY OF NEUROLOGY MEETING

Sheraton-Cadillac Hotel, Detroit, Michigan

NEUROPATHOLOGY—April 24, 1961. Dr. Erland R. Nelson. Fees: Juniors: $20.00; Fellows, Actives and Associates: $25.00; Non-members: $30.00. Deposit on slide box: $25.00 (all membership categories).

BASIC ELECTROENCEPHALOGRAPHY—April 24, 1961. Dr. Fernando Torres. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEUROCHEMISTRY—April 24, 1961. Dr. Maynard M. Cohen and Dr. Donald B. Tower. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

METABOLIC DISORDERS OF THE NERVOUS SYSTEM—April 24, 1961. Dr. Gilbert H. Glaser. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

ADVANCED CHILD NEUROLOGY—April 25, 1961. Dr. Michael E. Blaw and Dr. Paul M. Ellwood, Jr. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

THE ELECTRON MICROSCOPE AND THE NERVOUS SYSTEM—April 25, 1961. Dr. Augustus S. Rose. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEWER CONCEPTS OF HUMAN CEREBRAL ORGANIZATION—April 25, 1961. Dr. John S. Meyer. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

NEURORADIOLOGY—April 25, 1961. Dr. A. L. Sahs. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

ABNORMAL STATES IN NEUROPHYSIOLOGY—April 26, 1961. Dr. James L. O'Leary. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

ADVANCED ELECTROENCEPHALOGRAPHY—April 26, 1961. Dr. Frank Morrell. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

MEDICOLEGAL ASPECTS OF NEUROLOGY—April 26, 1961. Dr. Royal C. Gray. Fees: Juniors: $10.00; Fellows, Actives and Associates: $15.00; Non-members: $20.00.

In addition a special review course in Common Neurologic Diseases is offered to General Practitioners on Wednesday, April 26, 1961. The registration fee is ten dollars. Credit will be given by the American Academy of General Practice. This course is not available to members of the American Academy of Neurology. Dr. Benjamin Boshes is Course Chairman.

ENROLLMENT FOR ALL COURSES IS LIMITED

Priority will be determined by date of application.
No application will be accepted after April 14, 1961.

Applications will not be taken at the Sheraton-Cadillac Hotel in Detroit.

– – – – –

Outline of each course, application and further information may be obtained from

SPECIAL COURSES – AMERICAN ACADEMY OF NEUROLOGY
4307 East 50th Street, Minneapolis 17, Minnesota

one businessman has epilepsy...

even his colleagues need not know—if his seizures are adequately controlled—With proper medication, epileptics may achieve success in a wide variety of professions.*

for improved seizure control

DILANTIN®

SODIUM KAPSEALS® *outstandingly effective in* ***grand mal and psychomotor seizures***...DILANTIN Sodium *(diphenylhydantoin sodium, Parke-Davis) is available in several forms including Kapseals of 0.03 Gm. and of 0.1 Gm., in bottles of 100 and 1,000.*

other members of THE PARKE-DAVIS FAMILY OF ANTICONVULSANTS

for grand mal and psychomotor seizures: PHELANTIN® Kapseals *(Dilantin 100 mg., phenobarbital 30 mg., desoxyephedrine hydrochloride 2.5 mg.), bottles of 100.* ***for the petit mal triad:*** MILONTIN® Kapseals *(phensuximide, Parke-Davis) 0.5 Gm., bottles of 100 and 1,000; Suspension, 250 mg. per 4 cc., 16-ounce bottles* • CELONTIN® Kapseals *(methsuximide, Parke-Davis) 0.3 Gm., bottles of 100.*

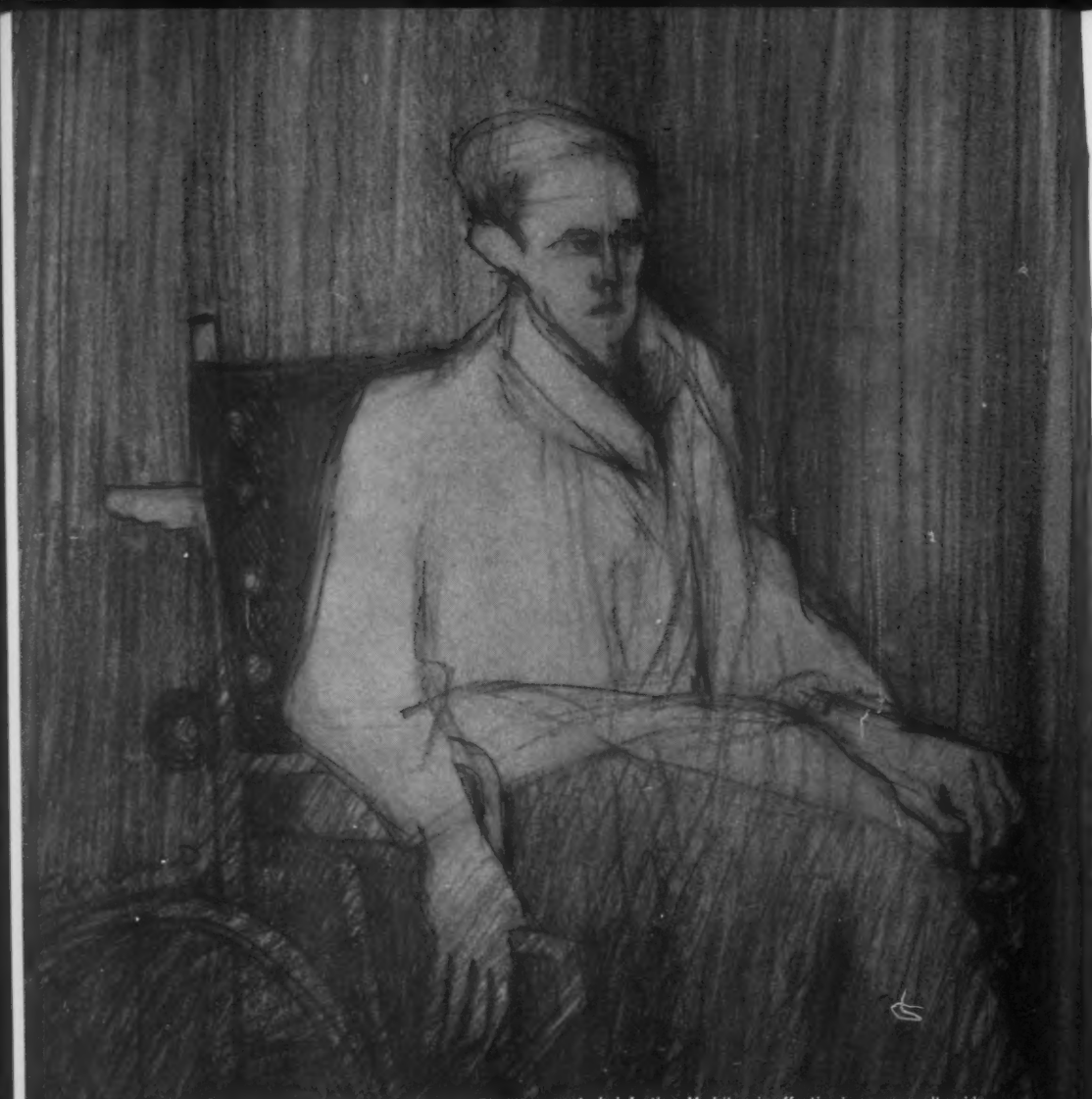
*Abraham, W., in Green, J. R., & Steelman, H. F.: Epileptic Seizures, Baltimore, Williams & Wilkins Company, 1958, p. 181

Literature supplying details of dosage and administration available on request.

27560

PARKE, DAVIS & COMPANY • Detroit 32, Michigan

PARKE-DAVIS



IN CORD BLADDER
long-term therapy with
MADRIBON
the safest long-acting sulfonamide

"... especially useful for long-term therapy required in persistent chronic infections."[1]

MADRIBON® — 2,4-dimethoxy-6-sulfanilamido-1,3-diazine

controls infection Madribon is effective in an unusually wide range of pathogens, including some antibiotic-resistant strains. "Excellent"[2] results were obtained in a group of 35 paraplegics—all with cord bladders, chronic cystitis and some degree of pyelonephritis for up to 15 years. During a full year on Madribon, despite **in vitro** resistance, none "... exhibited the clinical signs of bladder infection."[3]

safely With Madribon therapy, the incidence of side effects is exceptionally low – less than two per cent in over 15,000 reported cases. An impressive absence of side effects was especially noted in the extended treatment of paraplegics.[2,3]

economically Madribon is realistic therapy because of "... its effectiveness in low dosage and its long-acting potential."[2] The cost of Madribon "... is approximately one third that of the average antibiotic."[4]

References: 1. J. D. Young, Jr., W. S. Kiser and O. C. Beyer, **Antibiotic Med. & Clin. Therapy,** 6:(Suppl. 1), 53, 1959. 2. W. A. Leff, **ibid.,** p. 44. 3. R. E. Bagdon, L. O. Randall and W. A. Leff, **Ann. New York Acad. Sc.,** 82 (Art. 1), 3, 1959. 4. J. C. Elia, **ibid.,** p. 52.

Consult literature and dosage instructions, available on request, before prescribing.

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc.

NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

Augustus S. Rose, M.D., President
A. L. Sahs, M.D., President-Elect
Joseph M. Foley, M.D., Vice-President
Robert Utterback, M.D., Secretary
Charles M. Poser, M.D., Treasurer

JANUARY 1961

ARNMD Holds Its Fortieth The Association for Research in Nervous and Mental Disease held its fortieth annual meeting in New York, December 9 and 10. According to its President and Chairman of the Commission, Saul R. Korey, this year's subject was devoted to a consideration of certain aspects of the "ultrastructure and metabolism of the nervous system." "It is not a new era into which we enter," said Korey, "but rather one in which methods and theories found useful in the biological and physical sciences are being applied to the study of the unique properties of the nervous system. With the advent of greater knowledge about the brain, distinctions of the organic and the functional may pass into history and we may all escape our private Babal." To demonstrate this theme, a series of presentations were made by a carefully selected array of talent from the United States, Canada, and England. In the American group were some of the most renowned investigators in these fields, among them: Sarah A. Luse (St. Louis); J. H. Menkes (Baltimore); J. D. Robertson (Waverly, Mass.); M. M. Rapport (New York); R. E. McCaman (Indianapolis); D. B. McDougal, Jr. (St. Louis); J. H. Austin (Portland); Margery B. Lees (Waverly); H. Ferandez-Moran (Boston); J. Axelrod (Bethesda); E. Roberts (Duart, Calif.); H. A. Waisman (Madison); S. S. Kety (Bethesda); A. Szent-Gyorgyi (Woods Hole); G. C. Cotzias (Upton, N. Y.); L. E. Hokin (Madison); S. Ehrenpreis (New York); D. A. Hamburg (Bethesda); and F. Elmadjian (Shrewsbury, Mass.). Among the visitors were: E. B. Chain (Rome); H. McIlwain (London); J. H. Quastel (Montreal); D. Richter (Surrey); and G. W. Harris (London).

Epilepsy Society Convenes at Waldorf The day before the ARNMD meeting at the Roosevelt Hotel, members of the American Epilepsy Society convened at the Waldorf-Astoria (December 8) under the presidency of Peter Kellaway of Houston, Texas. The scientific sessions were devoted primarily to changing concepts of focal epilepsy in their neurophysiological and neurosurgical aspects. The major symposium was moderated by Herbert Jasper (Montreal). Theodore Rasmussen (Montreal) spoke on "Changing Concepts in the Treatment of Focal Epilepsy," and Jasper presented the physiological implications. Clinical EEG considerations were discussed by Cosimo Ajmone-Marsan (Bethesda), and the symposium discussion was directed by A. Earl Walker (Baltimore). The presidential address, given by Peter Kellaway, was on "Seizures Associated with Apnea and Cardiac Arrest."

National Congress Held in Mexico City The Hotel Del Prado in Mexico City was the scene on November 29 through December 3 of the First National Congress of Neurological and Psychiatric Sciences, held under the direction of Agustin Caso, executive president, and Humberto Mateos and José Ma. Sánchez Cabrera, secretaries. The sessions were organized by the Mexican Societies of Neurology and Psychiatry, Neurological Surgery, Psychoanalysis, Electroencephalography and the Mexican Association of Psychoanalysis. The scientific sessions of the Congress, December 2 and December 3, covered a wide range of topics in the fields of neurology and psychiatry. Among the notables listed on the program were: Arturo Rosenblueth, Carlos Guzmán-Flores, Juan Cárdenas, Santiago Ramirez, Ramón del Fuente, Isaac Costero, José Humberto Mateos, Hernando Guzmán West, Julio Hernández Penich, Jean Delay (Paris), and many others. From the United States were: E. B. Sigg (New York); N. A. Buchwald (Calif.); D. Taxdal (Baltimore); and S. Ervin and Verno Mass (Mass.).... Prior to the Congress, review courses were held November 30 to December 1 on Recent Advances in Neurology, Psychiatry, and Electroencephalography.

Training Fellowships in Neuroanatomy and Neurophysiology Louis Hausman announces that the New York University Medical Center is offering training fellowships with stipends of about $1,000 in neuroanatomy and neurophysiology beginning March 1, 1961. To be eligible, candidates must hold an M.D. or Ph.D. degree and be interested in teaching or research in these subjects. Applications should be submitted by February 1, 1961. Inquiries should be sent to Dr. Louis Hausman, Department of Anatomy, New York University Medical Center, 550 First Avenue, New York 16.

Jasper Becomes IBRO Secretary Herbert Jasper, of the Montreal Neurological Institute, was recently elected Executive Secretary General of IBRO (International Brain Research Organization); Heinrich Waelsch (New York) was elected treasurer; and the members of the IBRO's executive committee are: P. Anokhin (USSR); A. Fessard (France); G. W. Harris (England); H. W. Magoun (Calif.); G. Moruzzi (Italy); and G. D. Smirnov (USSR). Their alternates are: A. Brodal (Norway); D. Bovet (Italy); W. A. Rosenblith (USA). The structure and objectives of the IBRO program were outlined on December 7, 1960, by Dr. Jasper at an informal meeting in the Hotel Roosevelt, New York. Present at the meeting were: Drs. Jasper, Waelsch, Brazier, T. Rasmussen (Montreal), and L. Kurland. Also present were: Drs. R. Masland, representing NINDB, and P. Bailey, representing the World Federation of Neurology.... The Secretariat of IBRO is located in UNESCO House in Paris. Its affairs are under the direction of the Executive Secretary and a central committee composed of selected members of several scientific panels.

IBRO Envisages Interdisciplinary Approach

Perhaps the cardinal feature of the IBRO's projected program is coordinating of interdisciplinary basic brain research on an international level. At the first meeting of IBRO's Central Committee, held in Paris October 3-7, 1960, it was recommended that its program include a project of fellowships and exchange of scientific workers; the organization of temporary interdisciplinary research teams to attack common problems; promotion of world-wide education on brain research by means of seminars, by means of training courses conducted by visiting scientists; on extension of existing laboratory facilities throughout the world; the dissemination of scientific information and news about basic brain research through the compilation of a directory of laboratories and the publication of a bulletin, giving brief reports of research in progress and news of scientific events; and the development of a restricted number of symposia for which special needs exist....The concept of an international brain institute had been under consideration by UNESCO since 1946, but no action was taken until an international symposium on brain waves and behavior was held in Moscow, October 6-11, 1958, when an international working committee was established by the president of the International Federation of Societies of Encephalography and Clinical Neurophysiology. Then at a meeting at UNESCO House under the auspices of CIOMS on October 2-3, 1959, this committee was enlarged by representatives from neuroanatomy and neurochemistry. The preliminary staff and organizational work of IBRO was carried on by Dr. Jean Delafresnaye of CIOMS at the request of UNESCO and the executive committee of CIOMS.

Report on London Conference Will Highlight AAMD Meeting

Reports on various phases of the recent London Conference on the scientific study of mental deficiency will be made at a forthcoming sectional meeting of the American Association on Mental Deficiency. Speaking at the AAMD meeting, to be held in Cincinnati on May 2-3, will be NINDB Director Richard L. Masland; Dr. Samuel A. Kirk, Director of the Institute for Research on Exceptional Children, University of Illinois; and Dr. William Sloan, Superintendent of the State Colony and Training School; Pineville, La. Dr. Masland will report on the London conference's biological phase, Dr. Kirk on the education and vocational phases, and Dr. Sloan on the psyochological phase. The three scientists will emphasize the implications, the direction, and the areas requiring further study.

Wechsler Lecture Given by Critchley

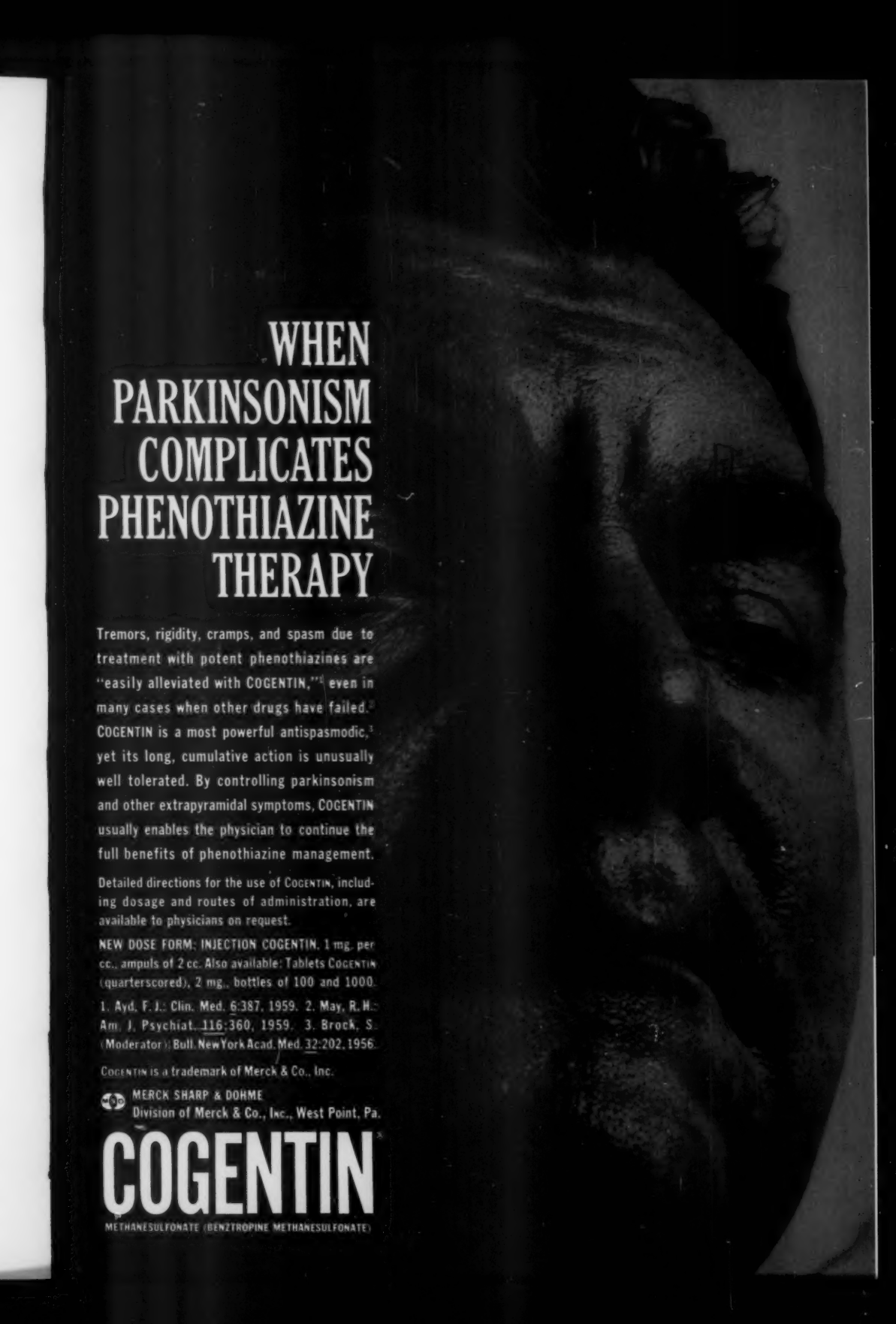
MacDonald Critchley, Senior Physician of the National Hospital for Nervous Diseases, Queen Square, London, and a Vice-President of the World Federation of Neurology, delivered the sixth annual Israel S. Wechsler Lecture at 8:30 p.m., December 9, 1960, in the Blumenthal

Auditorium of the Mount Sinai Hospital, New York City. His subject was "The Nature of Animal Communication and Its Relation to Language in Man."

Castaigne Appointed to Charcot Chair Professor P. Castaigne succeeded Professor Th. Alajouanine, now retired, as titular Professor of Neurology at the Salpêtrière in June 1960. Originally, the post was offered to Professor Pierre Mollaret, who, because of his responsibilities as Professor of Infectious Diseases at the Claude Bernard Hospital, requested this post be given to Professor Castaigne. This was the original Chair established for Charcot in 1862.... In January 1960, Professor Raymond Garcin became Professor of Clinical Neurology at the Salpêtrière, a new post of equal academic rank to the Charcot Chair.

Briefs Joseph M. Foley, AAN Vice-President, has left Seton Hall and will head the neurology program at Western Reserve in Cleveland.... Robert B. Aird is chairman of the joint committee of the AAN-ANA and American EEG Society on certification electroencephalographers.... A. L. Benton has been added to the editorial board of NEUROLOGY.... After 12 years of unstinting service to the AAN, Mrs. J. C. McKinley has resigned as Executive Secretary, as of December 31, 1960.... The AAN Board held its regular semi-annual meeting at the Hotel Roosevelt, New York, December 9, 1960, under the presidency of Augustus S. Rose.... Copies of the Report (PHS #800) on the 1958 NINDB-sponsored exchange mission in neurophysiology and neuropharmacology to the USSR, under the chairmanship of Francis M. Forster, are available upon request to the NINDB Information Office.... Professor Fred Grundy, Mansel Talbot Professor of Preventative Medicine in the Welsh National School of Medicine, Cardiff, Wales, has been appointed Assistant Director General of the World Health Organization.

Percy Bailey



WHEN PARKINSONISM COMPLICATES PHENOTHIAZINE THERAPY

Tremors, rigidity, cramps, and spasm due to treatment with potent phenothiazines are "easily alleviated with COGENTIN,"[1] even in many cases when other drugs have failed.[2] COGENTIN is a most powerful antispasmodic,[3] yet its long, cumulative action is unusually well tolerated. By controlling parkinsonism and other extrapyramidal symptoms, COGENTIN usually enables the physician to continue the full benefits of phenothiazine management.

Detailed directions for the use of COGENTIN, including dosage and routes of administration, are available to physicians on request.

NEW DOSE FORM: INJECTION COGENTIN, 1 mg. per cc., ampuls of 2 cc. Also available: Tablets COGENTIN (quarterscored), 2 mg., bottles of 100 and 1000.

1. Ayd, F. J.: Clin. Med. 6:387, 1959. 2. May, R. H.: Am. J. Psychiat. 116:360, 1959. 3. Brock, S. (Moderator): Bull. New York Acad. Med. 32:202, 1956.

COGENTIN is a trademark of Merck & Co., Inc.

MERCK SHARP & DOHME
Division of Merck & Co., Inc., West Point, Pa.

COGENTIN

METHANESULFONATE (BENZTROPINE METHANESULFONATE)

FROM: TECA CORPORATION

Devoted to development of electronic instrumentation for neuromuscular studies.

A NEW PORTABLE ELECTROMYOGRAPH, incorporating all facilities for nerve conduction time tests and Polaroid® photo-recording. The new Model B has been developed to supplement the 1 and 2 channel console Models TE1.2-7 and TE2-7. A matching console cabinet for the Model B can include an extended range magnetic tape recorder for operation with the EMG. The new portable, a compact one channel unit, will find application where the expandability, 2 channel facility, and flexibility of the TE console series are not required or where mobility is a prime requirement.

NEW NERVE CONDUCTION TIME FACILITIES in the Model B include unique time marker pulses superimposed electrically on the recording beam, permitting accurate direct measurement of conduction time, without error due to parallax or sweep and cathode ray tube distortions.

The stimulator, which generates rectangular pulses with 5 adjustable calibrated duration settings, provides high maximum output voltage (250V). The unique mounting of the intensity control on the percutaneous stimulator electrode handle now makes testing easier. Frequency of stimulus is adjustable from 1 per second to well into the tetanus range. An accessory conduction time indicator will permit direct reading of conduction time (or other physiological time intervals) from a digital indicator calibrated in milliseconds.

OTHER USEFUL FEATURES include a rugged Polaroid® camera mount that permits the camera to be instantly swung into position ready for use.

All electronic camera synchronization is fast, foolproof and easy to use for EMG or conduction time recording. The seven inch diameter flat face cathode ray tube is photographed thru an illuminated screen with engraved scale.

Advanced circuitry includes regulated power supplies for stability and accurate calibration, at low and high power line voltages. Radio frequency rejection circuits and 60 cycle filters are provided.

New Portable Model B with camera in retracted position.

OTHER NEW DEVELOPMENTS

An electromagnetic percussion hammer delivers uniform repeatable impacts to the body. The impact is synchronized with the sweep of the EMG so that muscle response, either electrical (EMG) or mechanical (motion velocity or acceleration) may be displayed as a stationary pattern on the screen, permitting accurate time measurements to be made, visually and by magnetic tape or photo-recording.

Continuous record high frequency multichannel photo-recorders for automatic operation in conjunction with the EMG. Permanent graphic records are provided with wide range of time scales and with integral time markers.

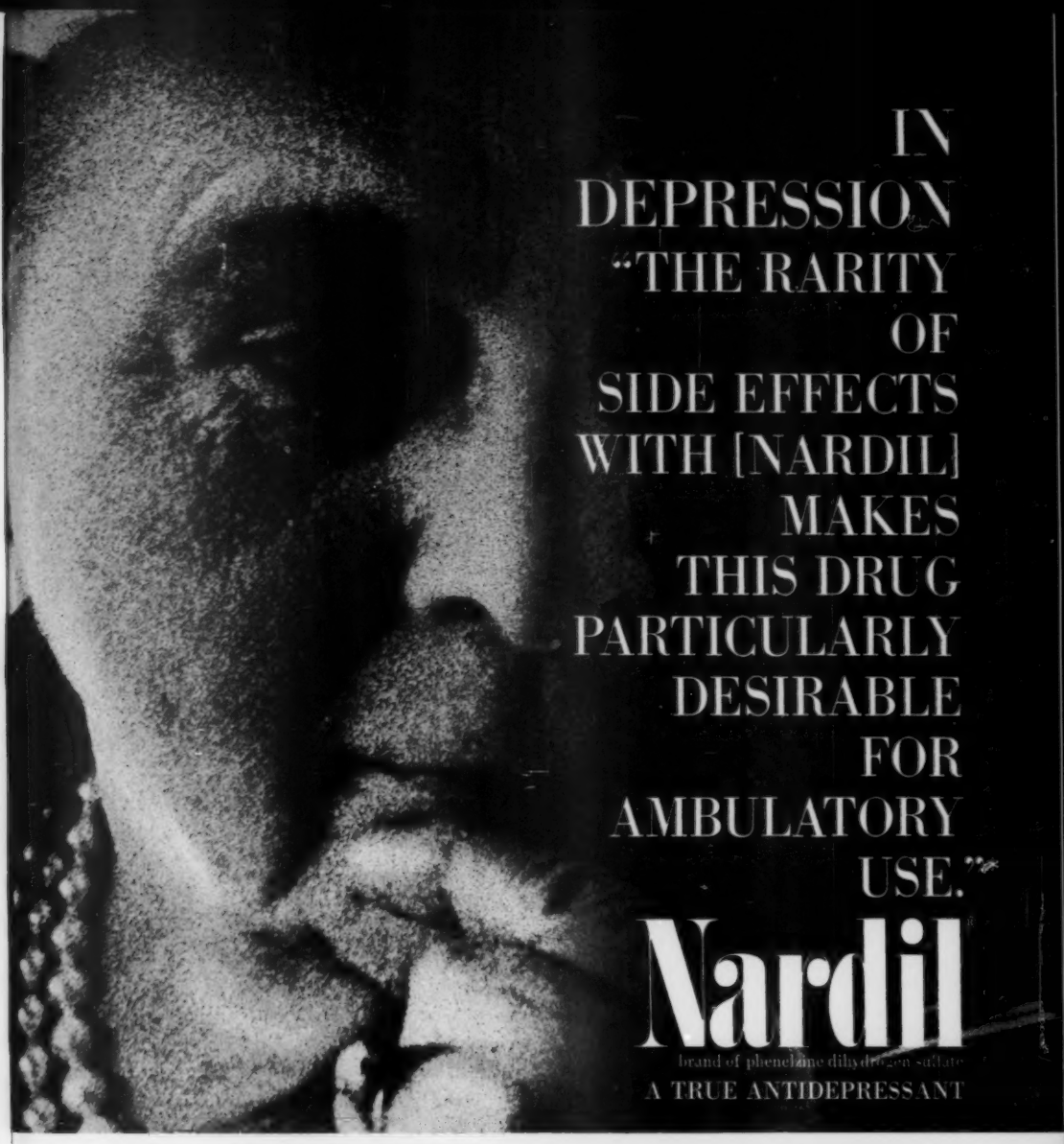
Electrical integrators for muscle potentials, with both averaging (adjustable decay) and absolute integral modes of operation.

Special stimulators for operation synchronized with the EMG, supplying electrically isolated pulse pairs with adjustable delay between each of the two independent outputs. Isolators can be supplied to users of Teca Chronaximeters to permit EMG recording of evoked potentials.

Also for electrodiagnosis, the Teca Model CH-3 a true stabilized current variable pulse generator and chronaximeter. Generates accurate rectangular pulses of current entirely independent of variations in patient or electrode impedance over a wide range. Incorporates many innovations for simplified accurate strength duration curve and chronaxie procedure. *Write for Bulletin.*

80 MAIN STREET, WHITE PLAINS, NEW YORK

TECA CORPORATION



IN DEPRESSION "THE RARITY OF SIDE EFFECTS WITH [NARDIL] MAKES THIS DRUG PARTICULARLY DESIRABLE FOR AMBULATORY USE."*

Nardil

brand of phenelzine dihydrogen sulfate

A TRUE ANTIDEPRESSANT

"Based on the results of a clinical trial with 150 ambulatory private patients, [Nardil]... has been highly effective in relieving severe depressive states."*

Nardil is rapidly effective—antidepressant response may be seen in a week, although complete remissions usually take from two to six weeks of continuous therapy.

"[Nardil] has distinct advantages...primarily because of the relative absence of side effects..."*

Nardil has an excellent safety record—established by over 100 scientific reports, and confirmed by a minimal incidence of toxicity in more than several hundred thousand patients to date.

Full dosage information, available on request, should be consulted before initiating therapy.

*Furst, W., M.D., F.A.P.A. (Attending Neuropsychiatrist, East Orange General Hospital, East Orange, N. J.): Psychopharmacological or Electrical Therapy of Severe Endogenous Depression, *J. M. Soc. New Jersey* 57:3 (March) 1960.

WARNER CHILCOTT

MORRIS PLAINS, N.J.

P511

makers of TEDRAL DELUSIL PROLOID PERITRATE MANDELAMINE

CARE and TRAINING for the MENTALLY RETARDED CHILD

The Training School at Vineland provides care and treatment for boys and girls 2 years or older with mental potential of 6 years. Complete professional staff. Electroencephalographic, and neurological examinations, individual psychiatric, psychological, physiological, and speech observations and therapies.

SIX COMPREHENSIVE PROGRAMS:

- Observation and Diagnosis
- Education and Training
- Custodial Care
- Residential Supervision
- Summer Program
- Psychiatric Treatment Center

The educational program aims at maximum development of each child. Training includes self-care; group living; formal classroom education; development of practical habits, attitudes and work skills. Children live in homelike cottages on 1600-acre estate. School, hospital, chapel, swimming pools, lake, working farm. The Training School Research Laboratory is famed for continuous study of causes, prevention and treatment of mental retardation. Established 1888. For information write: Registrar, Box Q,

THE TRAINING SCHOOL AT VINELAND, NEW JERSEY

A private, non-profit residential center for the care and treatment of the mentally retarded

MENTAL RETARDATION PROGRAM DIRECTOR FOR MICHIGAN DEPARTMENT OF MENTAL HEALTH

Annual salary—$21,402 to $25,682. This is a new position and will involve the administering of treatment, rehabilitation, and training programs for the mentally retarded, including the epileptic.

MINIMUM QUALIFICATIONS: Three years of professional experience in the treatment of the mentally retarded subsequent to obtaining a diplomate in psychiatry or pediatrics and possession of license to practice medicine in Michigan. (Out-of-state applicants must be qualified for and obtain Michigan license as soon as possible, if appointed.) Two years of experience must have been in an administrative capacity.

Position is in the Michigan civil service. Basis of examination will be either an evaluation of education and experence or an oral examination designed to test for knowledge of the principles and practices of medicine and surgery; the principles and practices of psychiatry as applied to mental retardation; and the ability to direct a broad program for the mentally retarded on a state-wide basis. If an oral examination is held, it will be at a place most convenient to the applicants and the oral board. Applicants notified to appear for the oral examination must pay their own expenses.

Applications for this position will be accepted until and including January 11, 1961.

Application forms and further information may be obtained by writing to the

MICHIGAN CIVIL SERVICE COMMISSION
Third Floor, Lewis Cass Building
Lansing 13, Michigan

THE UNIVERSITY OF MICHIGAN MEDICAL CENTER

Postgraduate Course in

CLINICAL NEUROLOGY

UNIVERSITY HOSPITAL
Ann Arbor, Michigan

March 13 and 14, 1961

The postgraduate course in Clinical Neurology for the current year is devoted almost exclusively to a survey and appraisal of current aspects of treatment—treatment not only of those neurologic conditions most frequently encountered by the practicing physician, but also of those complications of systemic disease that affect the nervous system. Although differential diagnosis and special diagnostic procedures will obviously be mentioned and discussed, stress will at all times be placed upon therapy.

Program and application form may be obtained from

JOHN M. SHELDON, M.D., *Director*
Department of Postgraduate Medicine
University Hospital, Ann Arbor, Michigan

If you Change

YOUR ADDRESS

Won't you please notify us as far in advance as possible. Send your old address together with the new.

Copies mailed to your old address will not be forwarded by the Post Office unless you provide the Post Office with the forwarding fee.

Send your change of address to

NEUROLOGY
84 South 10th St.
Minneapolis 3, Minnesota

Proven

in over five years of clinical use and
more than 750 published clinical studies

Effective

for relief of anxiety and tension

Outstandingly Safe

- simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation
- no cumulative effects, thus no need for difficult dosage readjustments
- does not produce ataxia, change in appetite or libido
- does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
- does not impair mental efficiency or normal behavior

Miltown®

meprobamate (Wallace)

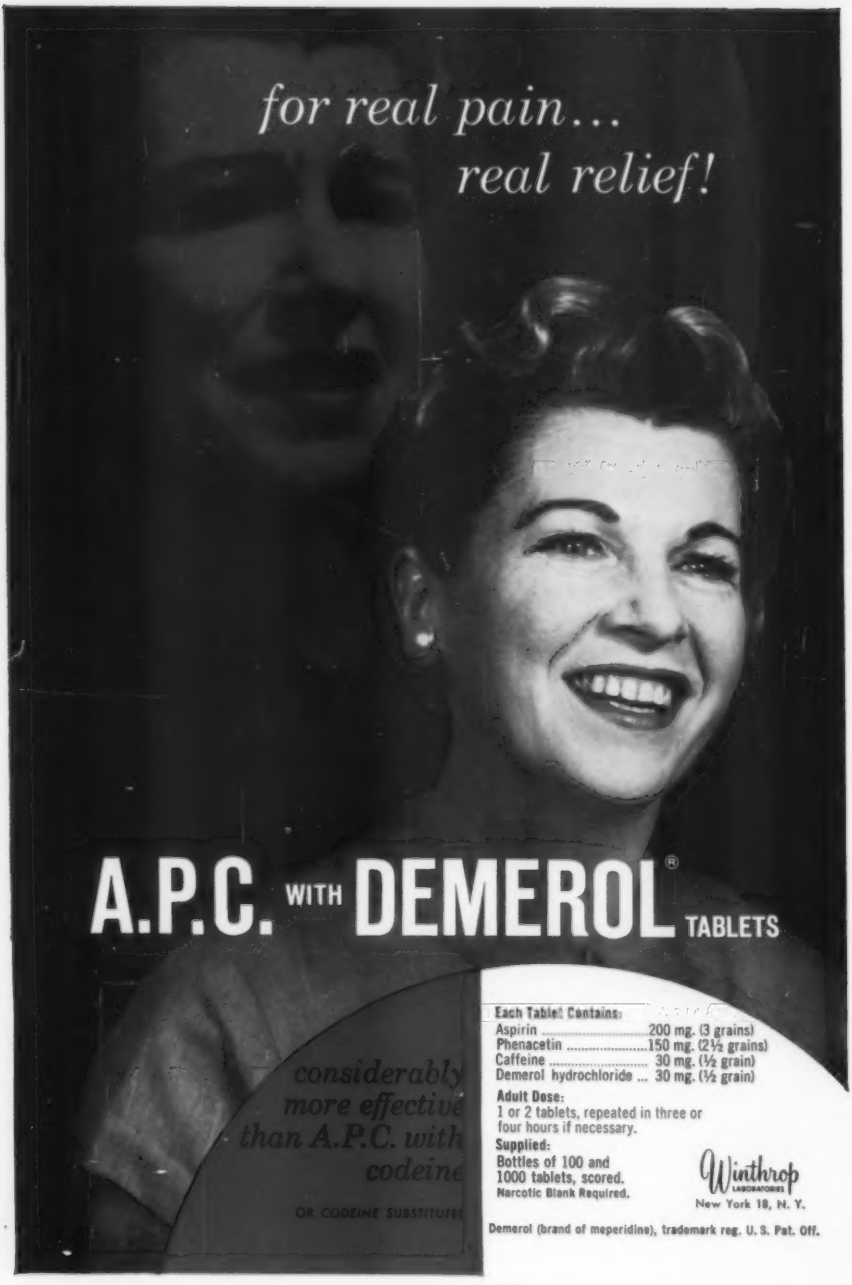
Usual dosage: **One or two 400 mg. tablets t.i.d.**

Supplied: **400 mg. scored tablets, 200 mg. sugar-coated tablets; or as MEPROTABS®— 400 mg. *unmarked*, coated tablets.**

WALLACE LABORATORIES / *Cranbury, N. J.*

OH-2058

®TRADE-MARK


for real pain...
real relief!
A.P.C. WITH DEMEROL® TABLETS
considerably
more effective
than A.P.C. with
codeine
OR CODEINE SUBSTITUTE
Each Tablet Contains:
Aspirin ..... 200 mg. (3 grains)
Phenacetin ..... 150 mg. (2½ grains)
Caffeine ..... 30 mg. (½ grain)
Demerol hydrochloride ... 30 mg. (½ grain)
Adult Dose:
1 or 2 tablets, repeated in three or four hours if necessary.
Supplied:
Bottles of 100 and 1000 tablets, scored.
Narcotic Blank Required.
Winthrop LABORATORIES
New York 18, N. Y.
Demerol (brand of meperidine), trademark reg. U. S. Pat. Off.